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GRANT NUMBER: DAMD17-94-J-4512

TITLE: Development and Demonstration of a Networked Telepathology 3-D Imaging, Databasing, and Communication System

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REPORT DATE: October 1996

TYPE OF REPORT: Final

PREPARED FOR: Commander
U.S. Army Medical Research and Materiel Command
Fort Detrick, Frederick, Maryland 21702-5012

REPORT DOCUMENTATION PAGE

Form Approved
OMB No. 0704-0188

1. AGENCY USE ONLY *(Leave blank)*	2. REPORT DATE	3. REPORT TYPE AND DATES COVERED
	October 1996	Final (1 Oct 94 - 30 Sep 96)

4. TITLE AND SUBTITLE
Development and Demonstration of a Networked Telepathology 3-D Imaging, Databasing, and Communication System

5. FUNDING NUMBERS
DAMD17-94-J-4512

6. AUTHOR(S)
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8. PERFORMING ORGANIZATION REPORT NUMBER

9. SPONSORING/MONITORING AGENCY NAME(S) AND ADDRESS(ES)
Commander
U.S. Army Medical Research and Materiel Command
Fort Detrick, Frederick, Maryland 21702-5012

10. SPONSORING/MONITORING AGENCY REPORT NUMBER

11. SUPPLEMENTARY NOTES

12a. DISTRIBUTION / AVAILABILITY STATEMENT
Approved for public release; distribution unlimited

12b. DISTRIBUTION CODE

13. ABSTRACT *(Maximum 200)*

Final project results and recommendations for future DoD research relating to digital pathology systems for military purposes are given in this report. The following areas were addressed: 1) 2-D and 3-D Virtual Slide (VS) systems for pathology applications; 2) Evaluation and testing of workstations and operating systems for digital pathology applications(DP); 3) Testing and demonstration of networking and internet technologies for Digital pathology and telepathology (TP) purposes; 4) Evaluation, specification and testing of an appropriate Object-Oriented Database Management System (OODMS) for DP and TP purposes; 5) Evalutation, testing, and recommendation of a hierarchical storage management system (HSM) for DP image recovery for local and TP referral basis; 6) Integration of National Library of Medicine (NLM) medical language resources (e.g. UMLS and SNOMED) to pathology image files to enable content-based retrieval; 7) Commercial partnership considerations in DP and TP; and 8) Final recommendations.

14. SUBJECT TERMS
Telepathology, anatomic pathology, image databasing.

15. NUMBER OF PAGES
103

16. PRICE CODE

17. SECURITY CLASSIFICATION OF REPORT	18. SECURITY CLASSIFICATION OF THIS PAGE	19. SECURITY CLASSIFICATION OF ABSTRACT	20. LIMITATION OF ABSTRACT
Unclassified	Unclassified	Unclassified	Unlimited

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NA In the conduct of research involving hazardous organisms, the investigator(s) adhered to the CDC-NIH Guide for Biosafety in Microbiological and Biomedical Laboratories.

B A Gatling Feb 4 1997

PI - Signature Date

Final Report-1996: DAMD17-94-J-4512

"Development and Demonstration of a Networked Telepathology 3-D Imaging, Databasing, and Communication System: Phase I"

TABLE OF CONTENTS

INTRODUCTION

The overarching goal of this project was to pursue a broad experimental program in research focusing on a successful implementation and integration of futuristic digital pathology (DP) and telepathology (TP) systems for Anatomic Pathology (AP). Further, special attention was paid to system use in military medical settings, which demands the linking of reference laboratories such as the Armed Forces Institute of Pathology (AFIP) to far-forward MASH facilities, ships, etc. The system was envisioned to have "store and forward" and interactive capability. The specific project focus evolved during the two year period as the knowledge and understanding of the practicing pathologist became better understood by Project Director Dr. Athey, who is not a pathologist, but instead a computerized-microscope imaging specialist. The practicing pathologist views the system in a graphical form on his or her workstation screen as shown in Figure 1. The goal of this project was to specify and assemble a high-end distributed 2-D and 3-D pathology imaging system, and to study its operating characteristics. This is the final report of this two year

Figure 1: Graphical User Interface (GUI) of the distributed University of Michigan DP System. The underlying technologies to enable such an application to be realized in a distributed and heterogeneous imaging and computing environment were the subject of this effort, linking the presentation, application, database, and physical layers of a prototype pathology local area network (LAN).

effort. For project background, please see the 1995 annual report. An excellent recent review of DP and TP systems has been published by Aller and Balis (1996). The work reported here was presented as a plenary lecture in the First Annual Meeting of Anatomic Pathology, Imaging, Informatics, and the Internet held in Pittsburgh, PA, in November, 1996.

This report details final project results and recommendations for future DoD research relating to digital pathology systems for military purposes. The following areas were addressed: 1) 2-D and 3-D Virtual slide (VS) systems for pathology applications; 2) Evaluation and testing of workstations and operating systems for digital pathology (DP) applications; 3) Testing and demonstration of networking and internet technologies for digital pathology and telepathology (TP) purposes; 4) Evaluation, specification, and testing of an appropriate Object-Oriented Database Management System (OODBMS) for digital pathology purposes; 5) Integration of National Library of Medicine (NLM) medical language resources (e.g. UMLS and SNOMED) to pathology image files to enable content-based retrieval; 6) Commercial partnership considerations in DP and TP; and 7) final recommendations.

BODY

Methods

As an aid to evaluating progress, the following list is taken from page 7 of the original proposal of Grant No. DAMD17-94-J-4512.

1. Install Viz-lab software on Indy. Link Inovision software on DMSV network and into Indy. Demonstrate color segmentation locally in kidney biopsy images.
2. Load header information and multimedia objects into object oriented database. Test for recall of images using keywords located in metathesaurus.
3. Retrieve images from object-oriented database and mass storage mock-up over the network from AFIP.
4. Demonstrate semi-automated 3-D reconstruction, image filtering, and display using Inovision and Vizlab.
5. Migrate Meridian software onto UNIX platform. Mount microscope directly on Andrews File system (AFS). Install AFS in AFIP SGI engine.
6. Complete testing of Kodak Photo-CD image compression and pyramiding capability. Utilize across network.
7. Full system documentation. Talk to microscope with keyboard and retrieve thumbnails and pyramid to full resolution.
8. Repeat over network to/from AFIP.

In addition, I have added the following task to the Statement of work:

9. Develop and test 2-D and 3-D virtual slide (VS) imaging concept (please see 1995 Annual Report for description and justification).

Summarizing the above: Software was installed and developed to enable DP/TP work to be performed. H-P and Macintosh Platforms were utilized. 2-D and 3-D image processing was performed on images obtained using a digital Electron Microscope (EM) and Laser Scanning Confocal (LSCM) Microscope. Kidney and muscle specimens were imaged and processed. Custom software for the VS application was produced. Networking was performed using Netscape, allowing the world access to the system developed, not just AFIP. Micrograph headers were semi-automatically stripped and pertinent information was placed into a OODBMS. Images can be retrieved over the network using keywords from a

structured vocabulary based upon the NLM Unified Medical Language System (UMLS). Image data is stored on Hard disks, optical disks, and backed up on DLT magnetic tapes. No specific operating system at AFIP was modified nor was a system installed there. Kodak photo CD and image compression and pyramiding technology was not used, as it was not deemed competitive. Instead, custom pyramiding software was produced and JPEG image compression technology was used. Voice recognition and system linkage was not performed due to original underspecification, but instead proposed as a contract modification (see Appendix II, VI).

The following format will be used in this section. Task worked on with goal, followed by methods used.

1) 2-D and 3-D digital image acquisition and virtual slide (VS) systems for DP and TP:

A virtual slide (VS) application has been developed for use in telepathology (TP) and dynamic anatomic pathology for tissue diagnosis. Noesis Visilog and Meridian Instruments software for applications development was used instead of the Inovision and Viz-lab software that was originally specified. We have tested a system that generates a full 2-D image of a tissue using a digital Electron Microscope (EM) and computerized scanning stage, producing mosaics of up to 1400 1.5MB images 10 bit images. Software to create the mosaicing was produced by the Environmental Research Institute of Michigan (ERIM) and by programmers in my group. Briefly, images of highest magnification needed to give desired sampling rate on the object are collected on a programmable stage with 7-10% overlap. Stage coordinates provide the starting point for image alignment and refinement of overlap. Successive images are median filtered, made binary, and aligned using an octree search algorithm combined with cross correlation analysis. Successive 4x downsampling with optional and specifiable neighborhood filters allows for image pyramiding. We have also implemented a similar system to generate digital 24-bit color Light Microscopic (LM) images representing the entire 3-D volumetric length, width, and depth of histologic specimens. For this purpose, we used a Meridian Ultima 312 LSCM system to create the 3-D image blocks needed as input to a semi-automated mosaicing system developed along the same lines as for the case above.

2) Implementation and testing of a pathology image handling architecture and links to an Object-Oriented Database Management System (OODBMS) for DP reference facilities:

We have designed and implemented an image handling architecture for the Digital Microscopy and Scientific Visualization (DMSV) laboratory at the University of Michigan to manage the flow of DP data objects throughout our LAN and software environment. A schematic of this architecture is given in Figure 2 below.

Database design specifications were established for DP and the following principals were adhered to: 1) Hierarchical database design and implementation; 2) Hierarchical image data management facility; 3) Image coordinate capture for virtual slide (VS) application; 4) Micrograph naming conventions; and 5)Pathology data management. Three database management systems were used to prototype applications during this project. They were 1) FileMaker Pro (Microsoft Corporation; Redmond, WA); 2) Mini SQL (Shareware from UCal, Berkeley); and the Versant OODBMS (Versant Corporation; . Versant was chosen to be compatible with the TCIMS program platform of Dr. John Silva (DARPA). Simple prototypes of various functionalities were created using databases 1 and 2, populating them with a standard set of images, parameters, and extracted features. A master system using Versant was created around imaging applications which required production capability for

other projects occurring in my laboratory. The Versant developer's kit allows for a graphical programming environment, allowing relationships to be set graphical with lines, arrows, boxes, etc. An example of such a relationship network for DP imaging and anatomic pathology datahandling is shown in Figure 3 below.

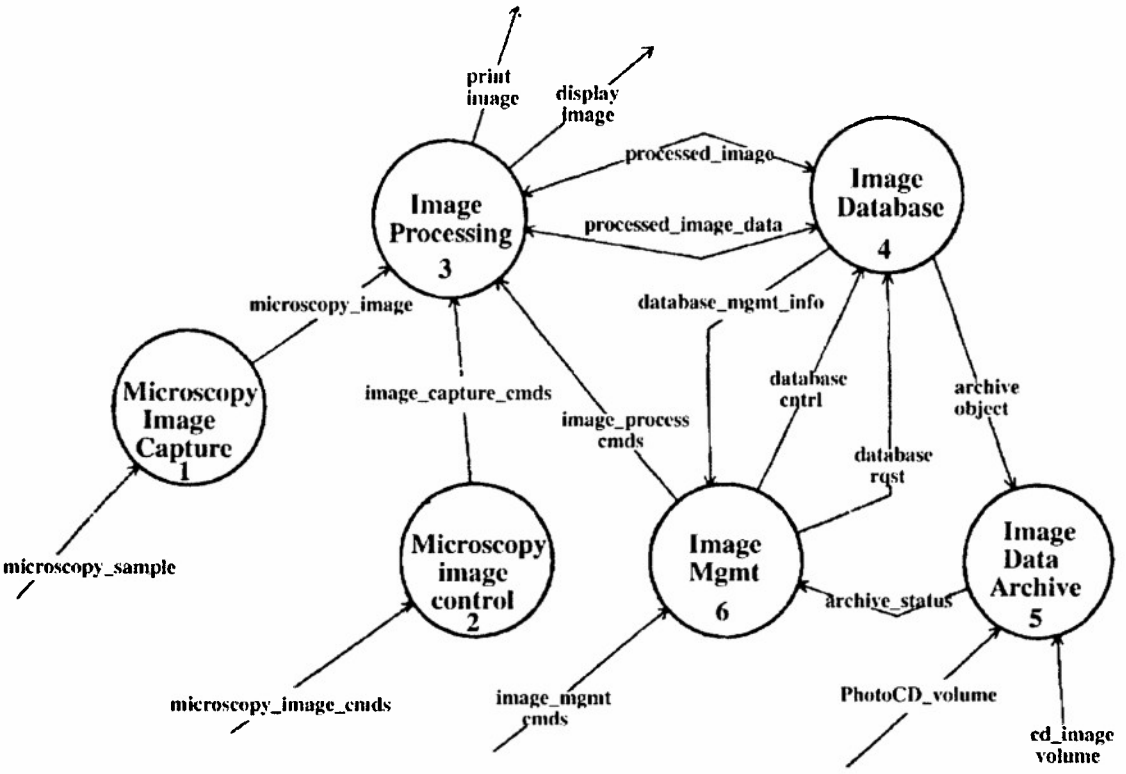

Figure 2: Schematic diagram showing linkages established in the laboratory to enable distributed DP and TP service. At this point, most of the links are operational. In the future, middleware can be implemented on DP LANs to capture microscope imagery, process it, database parameters and results, and archive the information selected to save.

3) Integration of National Library of Medicine (NLM) medical language resources (e.g. UMLS and SNOMED) to pathology image files to enable content-based retrieval:

We have developed a 2-fold strategy to using UMLS to retrieve medical imagery. The first part of the strategy involves constructing a controlled vocabulary that allows the microscopist to choose words and linkages that exist in the UMLS and in its associated semantic network. This is called a labeling interface (not shown, but soon to be installed on http://www.dmsv.med.umich.edu/). The labeling interface allows the user to choose the appropriate language descriptors from the mouse for the objects being imaged. The word stock for the labeling interface comes from the NLM UMLS ® Knowledge Sources, 8th Experimental Edition, January 1996. The word choice interface is hierarchical in nature, and so one chooses male/female, organ system, tissue type, cell, etc. Choices are prompted to the viewer and it is easy for this person to move around the body at will. This movement is facilitated by the second part of our labeling storage/retrieval strategy.

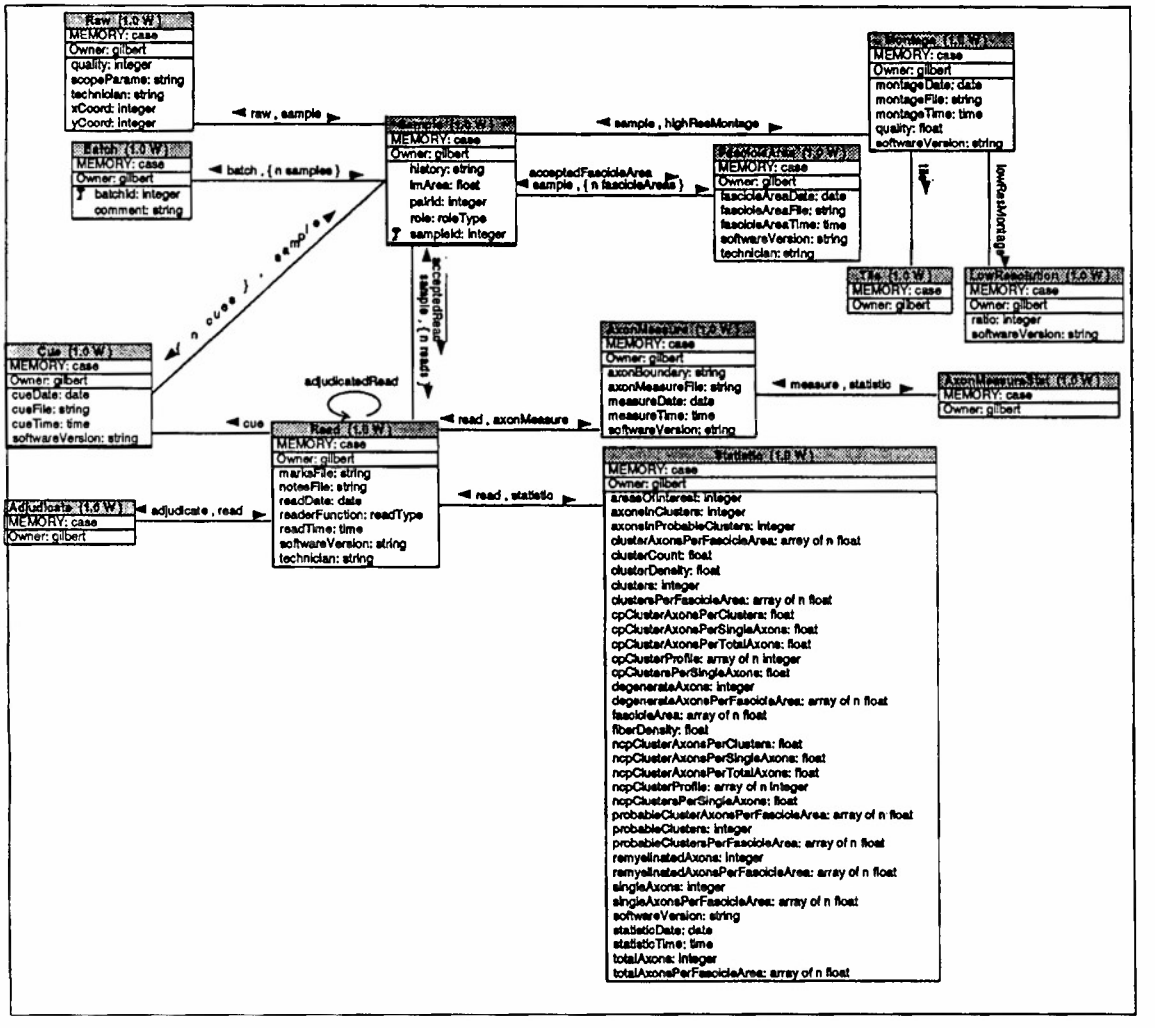

Figure 3: A view of the organization of the Versant OODBMS that was developed to track key VS parameters and selected features within the VS. In this case, images such as shown in Figure 4 were processed, labeling each individual axon cross section (black annuli in Figure 4c) for reader (expert) verification.

This second part relates to using the NLM visible human data sets as an entry point for data storage and retrieval. In another project in the laboratory, UMich gross anatomists have labeled a selected portions of the visible human and the spatial location of these labels is stored in a spatial index database on a server. If a set of images from a patient is desired, the name of the patient and the date will be sufficient to pull that data from the archive. But, if renal proximal tubules are desired (for example), one can point to the kidneys and drill to the renal tubules visually, or one can type or point to the UMLS term desired and the search engine embedded in the OODBMS will find the requested imagery and que it to the user for further analysis. This application was coded in Java Script . Several UNIX servers are

employed in the process. A system like this is a truly distributed computing application, and can be replicated on several microscopic input systems if they are programmed in the Windows NT Operating System. (Note: Microscope computers are invariably PCs).

4) Testing and demonstration of networking and internet technologies for DP and TP:

We rigorously tested this architecture (Figure 2) and OODBMS (Figure 3) in a production environment where ~10,000 images a day were made and processed for several weeks in succession. This production system is on a FDDI backbone, connecting several microscopes, display stations, and servers. Networking connections to the internet are T3.

Results

1) 2-D and 3-D digital image acquisition and virtual slide (VS) systems for DP and TP

We have tested a system that generates a full 2-D image of a tissue using a digital Electron Microscope (EM) and computerized scanning stage, producing VS mosaics of up to 1400 1.5MB images 10 bit images (Figure 4). We now use this system routinely in the imaging laboratory, routinely handling up to 2-2.5GB of VS data. Figure 5 shows the same VS software applied to 2-D LM datasets. Figure 6 shows results of the application of an extension to VS software that allows for the creation of 3-D VS microscopic image datasets, allowing the operator to "fly through" the tissue in x,y,z.

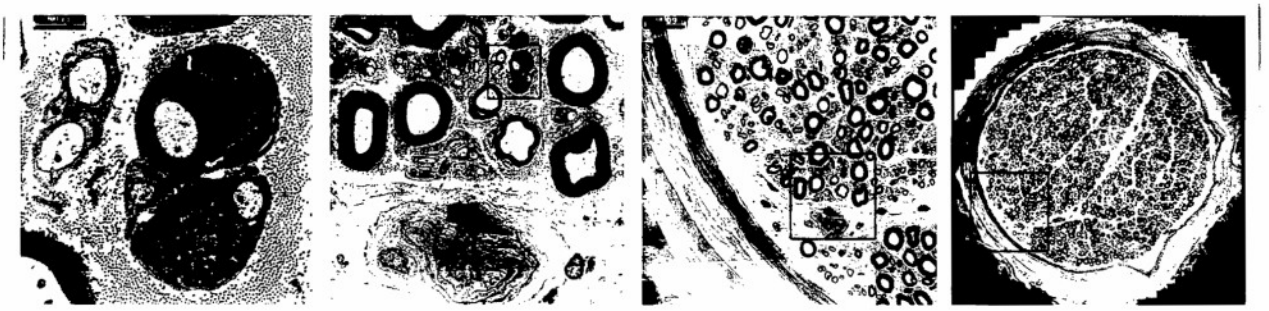

Figure 4: Nested composite EM VS montage of a 1.5mm human sural nerve cross-section composed of ~1500 individual micrographs. Acquisition time, 4h; pre-processing and feature-extraction time, 4h (H-P workstations). Fascicle diameter = 1.5 mm.

2) Implementation and testing of a pathology image handling architecture and links to an Object-Oriented Database Management System (OODBMS) and for DP reference facilities:

In order to maintain project focus, we have only populated the database with images of the inner ear, kidney biopsy specimens, muscle fiber images, and sural nerve images. Features in the images can also be searched in several test cases. Micrograph headers and other useful information such as operator, time, date, tissue examined, etc. were successfully stripped and placed into the three database systems named in Methods. Operator name, date, other parameters, or tissue names entered through the labeling interface is operational. User generated interactive image processing data was also loaded. Multimedia information was not handled effectively, but is being addressed currently (in

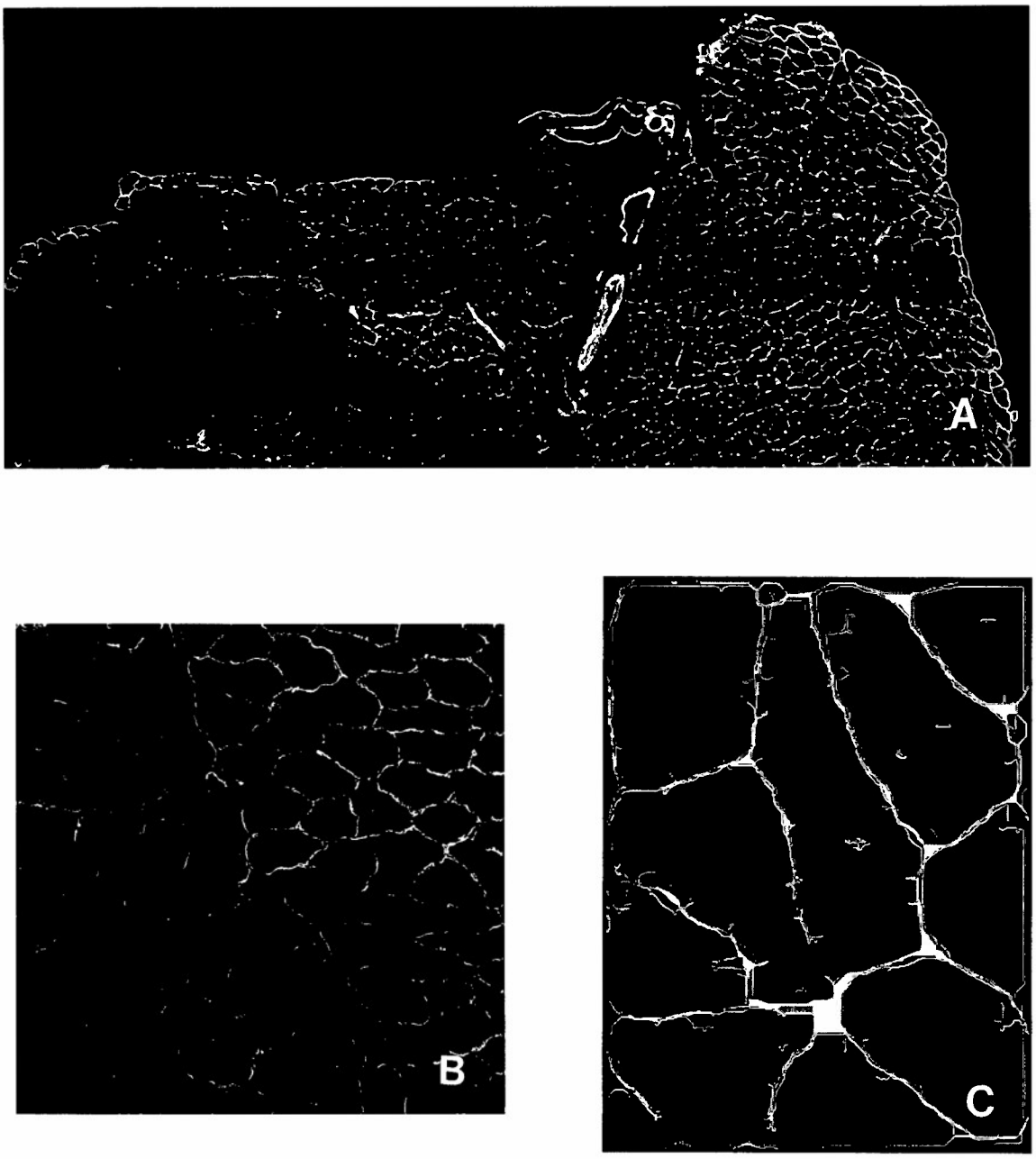

Figure 5: 2-D VS capability demonstrated for LM specimens. A) A 16-bit color image mosaic of a double-labeled muscle fiber bundle cross-section from the Rat EDL muscle, approx. 2.5 mm along the top. 52.5 images are shown out of approximately 150. Acquisition time = 1 hour for data shown. B) Higher resolution view of a 24-bit "chip" from the image. Boundaries describe individual muscle fascicles, 30-70 microns in diameter. C) High resolution processed image showing extraction (and database labeling) of myonuclei (blue). Nuclei lengths are 8-13 microns.

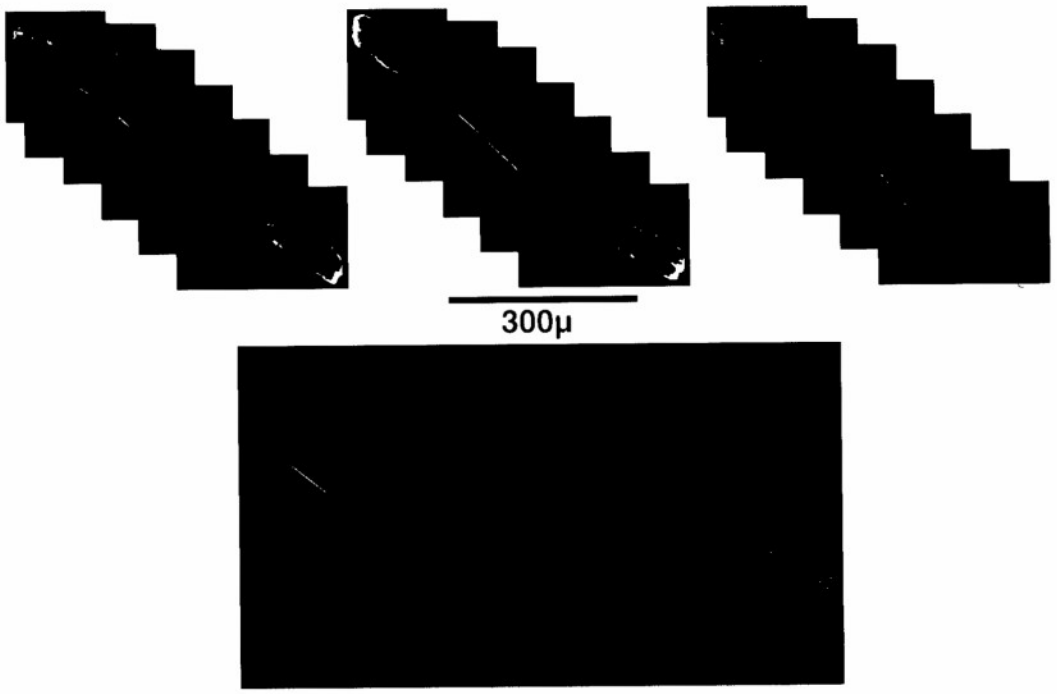

Figure 6: Two-channel, LSCM 3-D mosaic of an isolated muscle fiber, green = laminin, red = nuclei. The top view present three selected 1micron optical sections ranging from top to bottom of this thin and flattened (13 micron) fiber of length 0.8mm, 35 micron width. The bottom panel gives a selected volume-rendered view. Acquisition time, 2h; preprocessing, feature extraction time, estimated 1h to identify and label and database each of ~1500 nuclei.

another program) by using the Informix Universal Server Object-Relational DBMS (Informix Inc.; Menlo Park, CA).

3) Integration of National Library of Medicine (NLM) medical language resources (e.g. UMLS and SNOMED) to pathology image files to enable content-based retrieval:

Figure 7 below shows the UMich "Visible Human Database Locator", developed to access archived microscopic images through the net by sliding a finder over the anatomical area the image is related to (e.g., kidney) or by entering a UMLS (or a structured vocabulary term entered by the microscopist that links to UMLS. Once a first pass is made, a refined search on several parameters can be made, as shown in B). This web page can be found at http://www.dmsv.med.umich.edu/.

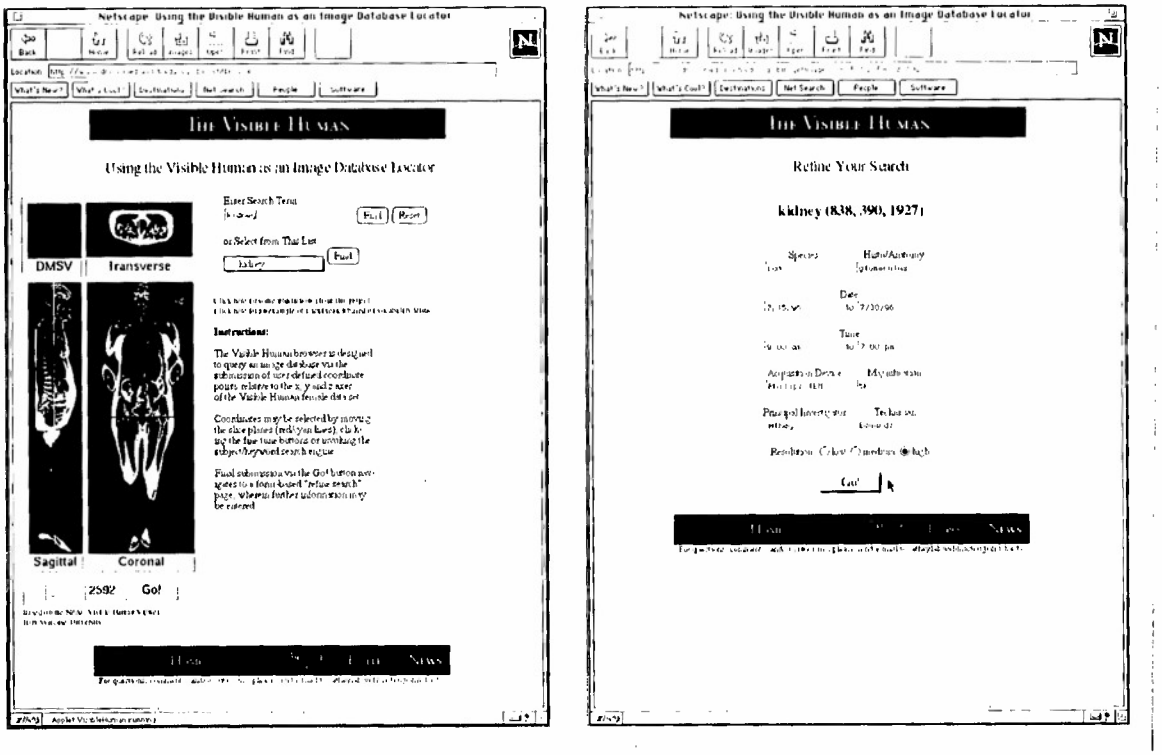

Figure 7: A) The UMich "Visible Human Database Locator", developed to access archived microscopic images through the net by sliding a finder over the anatomical area the image is related to (e.g., kidney). A UMLS search term can also be entered. Once a first pass is made, a refined search on several parameters can be made, as shown in B). This web page can be found at http://www.dmsv.med.umich.edu/.

4) Testing and demonstration of networking and internet technologies for DP and TP:

ATM LAN technology failed when we tested it under production imaging conditions. One problem we experienced with ATM was in integrating other networking modalities such as ethernet, 10- and 100 Base-T, and FDDI with ATM. We have tested the pathology CU-See Me modules (Dr. S. Erde, Cornell University Medical Center; NY) for interactive conferencing over the internet. One problem that we have had is the time it takes to recall large image VS slide mosaics from the data archive and to get the information transmitted through the LAN and then internet. Locally, 2 GB VS mosaics were routinely transmitted across the laboratory FDDI system in 30 minutes (~1MB/s, much slower than the expected ~8MB/sec!). Once on the fast-wide SCSI hard disk, data can be telescoped and scanned in near real time on a UNIX workstation with at least a 100 Mhz CPU and 256 MB of RAM. Low resolution (256x256x8bit) JPEG encoded image chips can be transmitted via the internet in near real time, searching a low resolution VS. High resolution (1024x1024x8bit) images can be retrieved in ~10 sec using standard (T1 or better) internet links. During high traffic periods, tests indicate that this transmission time

is increased to as long as 70 sec. Figure 8 shows examples of the objects retrieved from the internet browser.

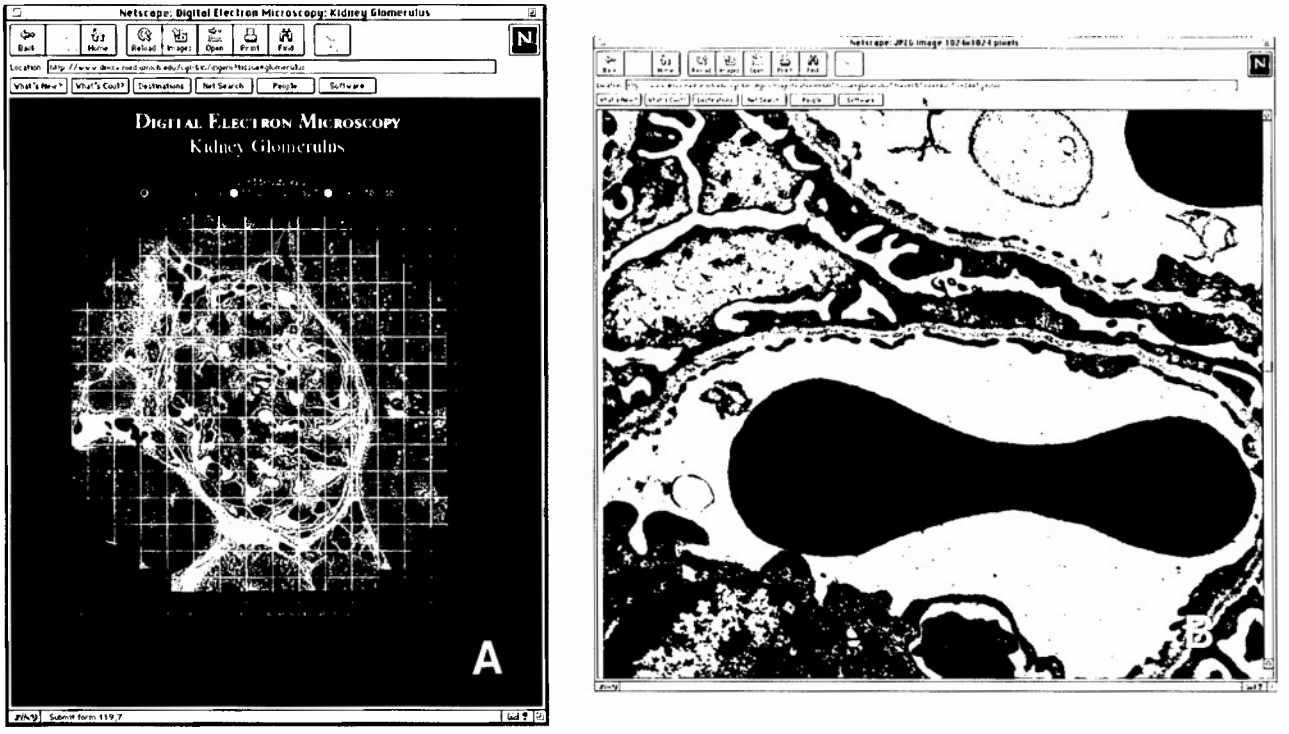

Figure 8: Output of VS through the Internet at low (A) and high (B) resolutions. These images are JPEG compressed for transmission. These VS images (and others) can be found at http://www.dmsv.med.umich.edu/.

CONCLUSIONS

Final Recommendations:

High resolution DP and TP systems are needed for effective military medical practice in an age of dwindling personnel and material resources. Ideally, a fully distributed and interactive dynamic DP system which is integrated and accessible over the internet and other secure networks is needed; including links to other parts of the distributed military personnel electronic patient record. Thus, I recommend further work in the following areas:

1. Real time specimen movement and control to enable a remote operator in the reference laboratory to control data acquisition; to be complementary to VS application.

2. Develop rapid image acquisition methodology for VS application.

3. Continued development of Netscape/Explorer integration and use of the Internet.

4. Integration of DICOM 3.0 and HL-7 communication standards (see W. Dean Bidgood, ImageSIG,HL7 homepage at DukeUniversity: http://www.mcis.

duke.edu/standards/HL7/sigs/imagemanagement/meetings/9601/KeyIssues.html). Integrate these standards with an extended and publicly available UMLS called VLST.

5. Investment in Pathology specific Picture Archiving and Communications Systems (PACS) designed around standards outlined in #3.

6. Use of Windows NT operating system to replace UNIX and Mac platforms.

7. Further investment in ATM network testing; partnering with qualified DP imaging environments.

8. Creation of middleware to link Pathology Laboratory Information Systems (LIS) to the anatomic imaging data to create a single DP report for transmission and archiving.

9. Development of Object/Relational database technology for pathology imaging applications. I have begun to use the Informix Universal Server system (Informix, Inc.; Menlo Park, CA).

In the spring of 1996, I submitted a detailed plan for continuation of this work to DARPA for consideration as a modification to this grant. These proposals are included in Appendix II ([A] Proposal Booklet Submitted to DARPA, and [B] Technical Proposal). As a proposed task, I suggested the choice of the Kurzwiel AI Voice Path ® Surgical/Anatomical Pathology System (Appendix VI).

Comment:

A big concern and disappointment that I had in this program was the lack of an ATM link to AFIP during the project period, as the increased bandwidth a multimedia functionality of ATM will be needed to make DP and TP practically realizable. In the original proposal and by explicit directive of ARPA Program Manager Dr. Satava, I was to establish the capability of an ATM link between UMich and AFIP via the ATD net hub at the Naval Research Laboratory (NRL). I worked tirelessly to enable this connection, making several trips to NRL, Walter Reed Army Medical Center (WRAMC), and AFIP; with and without Mr. Sam Montini of SAIC (ARPA contractor responsible for the links). The red-tape was a nightmare! I have one of the few facilities in the world to test this capability in a futuristic microscopic digital imaging environment. ARPA made several site visits to my facilities and joined with me to visit AFIP several times. Someone did a very poor job in procuring and delivering these necessary infrastructural enabling technologies into WRAMC/AFIP in a timely manner, and greatly limited the important work that I was funded and encouraged to perform. Once this connection is established, contracts and demonstration projects to rigorously test this capability should be let. A suitable partner would be a laboratory in an institution with NSF vBNS (very high seed networking backbone service--OC-3 to OC-12) development projects that are funded, making use of funded infrastructural development that is occuring in over 30 major universities and supercomputing facilities. The University of Michigan has recently been awarded the funding to join this experimental "Internet II", and my imaging lab will connect to it as it is an NSF recognized "meritorious" demonstration project for testing of this kind. I am sure that a few other DP imaging laboratories nationwide could be identified to help determine the need, bottlenecks, and barriers to successful military medical deployment of DP and TP service.

Commercial partnership considerations in DP and TP:

I am a firm believer in industry partnership with qualified corporations to reduce the cost of development, increase the probability of a successful product offering which will continue to be available over the long haul, and allow for a scaleable source of systems in time of conflict or disaster. For DP and TP systems, this means only four possible best qualified partners. These are 1) Nikon Corporation, Japan; 2) Olympus Inc., Japan; 3) Carl Zeiss, Germany; and 4) Leica; Germany. There are currently no American microscope manufacturers. All American DP and TP systems are integrated using components supplied by one of the four manufacturers listed above, usually by Value Added Reseller (VARs). Although all companies have a strong interest in DP and TP applications, I have found the Nikon group to be the most qualified. This group has been developing systems for the Japanese market for over a decade (see Appendix IV: "The Nikon HQ-130c Color Capture System for Telepathology"). Also, the Nikon team has tested their system in the clinical setting and have obtained preliminary evidence that the increased display resolution obtained using High Definition TV systems compared to NTSC video microscopic images correlates with fewer false cytological reads (see Appendix V: "Nikon A952 Project Results"). In addition, Nikon has recently established a US office for TP systems development and sales (Los Angeles; CA), and has placed a Development Engineer in Dr. Mun's laboratory at the ISIS center at Georgetown University.

REFERENCES/PRESENTATIONS

Aller RD, Balis UJ. Informatics, imaging, and the pathologist's workstation. In: Henry JB. ed. Clinical diagnosis and management by laboratory methods, 19th ed. Philadelphia: W.B.Saunders, 1996: 92-24.

This work was presented as a plenary lecture in the First Annual Conference on Pathology Imaging, Informatics, and the Internet held in Pittsburgh, PA, in November, 1996:

Athey, B.D. 1996. "A distributed system for Digital Imaging in Pathology" Informatics, imaging and the pathologist's workstation. In: Proceedings of the First Annual Conference on Pathology Imaging, Informatics, and the Internet, to be published.

The image database methodology was presented at the First Annual Conference on the Visible Human, US National Library of Medicine (NLM) in October, 1996:

Athey, B.D., A.J. Warner, J.C. Laby, , W.M. Meixner, J. Chung, J.P. Williams. 1996. Using the Visible Human as a Database Locator. The First Annual Conference on the Visible Human, US National Library of Medicine (NLM); to be published.

The VS work was also reviewed in a recent issue of Advanced Imaging (Reprint attached in Appendix III):

Grimm, L. (1996) "Daylight for Electron Microscopists" Advanced Imaging 11:6, 50.

The Journal of Supercomputing has invited Dr. Athey to submit a paper on the VS portion of this work, to be published spring, 1997.

PROJECT PERSONNEL

Project year 1995

Brian D. Athey, Ph.D.; Principal Investigator
Ms. Catherine Rector; Group Coordinator, Organizer
Geoffrey Guttmann, Ph.D.; 3-D Reconstruction, AFIP Coordination
Mr. M. Walter Meixner; System Design
Hugh Fogel; 3-D Imaging/Standards Testing
Mr. Jason Glick, Graphical Design
Mr. Brad Robertson: System Research Programmer, Computer System Administration
Mr. Justin Laby; System Research Programmer, Computer System Administrator
Mr. Phil Ray; Virtual Slide Development, Data Collection, World Wide Web Interface
Ms. Sari Failer, System Documentation

Project year 1996

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Ms. Sari Failer, Group Coordinator, Organizer Ms. Catherine Rector;
Mr. M. Walter Meixner; Technical Lead
Geoffrey Guttmann, Ph.D.; Object Labeling, VS and System Testing, Databasing
Ms. Jean Chung, UMLS Testing, Database Development
Mr. Gene Hsu, 2-D Image Processing
Mr. Jason Glick, 3-D Visualization, Project Illustration and Documentation

In addition, project support was provided by Mr. Justin Laby (System Research Programmer, Computer System Administrator) who was paid from a University of Michigan discretionary account. Also, database development and support was obtained form several graduate students from the UMich School of Information.

A1

FY 1996 Progress Report

APPENDIX 1

Strengths/Progress

~Large-scale 3-D microscopic data acquisition
~2-D and 3-D virtual slide
~Netscape integration
~Image file database/Search system
~Core graduate student cohort of ten (September 1996)
~3-D living microbioassay system (AASERT)
~Novel silicon biodetector 3-D imaging
~Major UMICH-SGI partnership in works

Weaknesses/Needs

~Working FORE system ATM switch
~SGI software for visualization/flythrough
~Modest video equipment/production budget
~Reasonable object-oriented database program

Brian D. Athey, PhD

July 21, 1996

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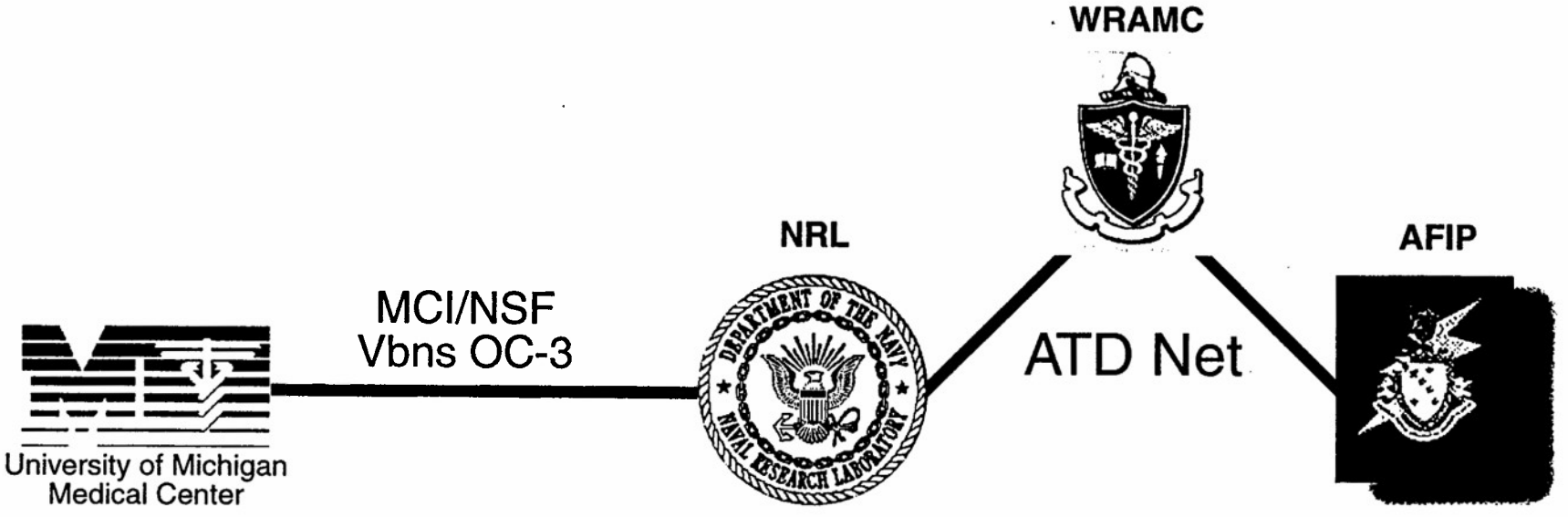
Proposed DARPA FY 1997
ATM Pathology Demonstration



[redacted]
~Hardware Integration

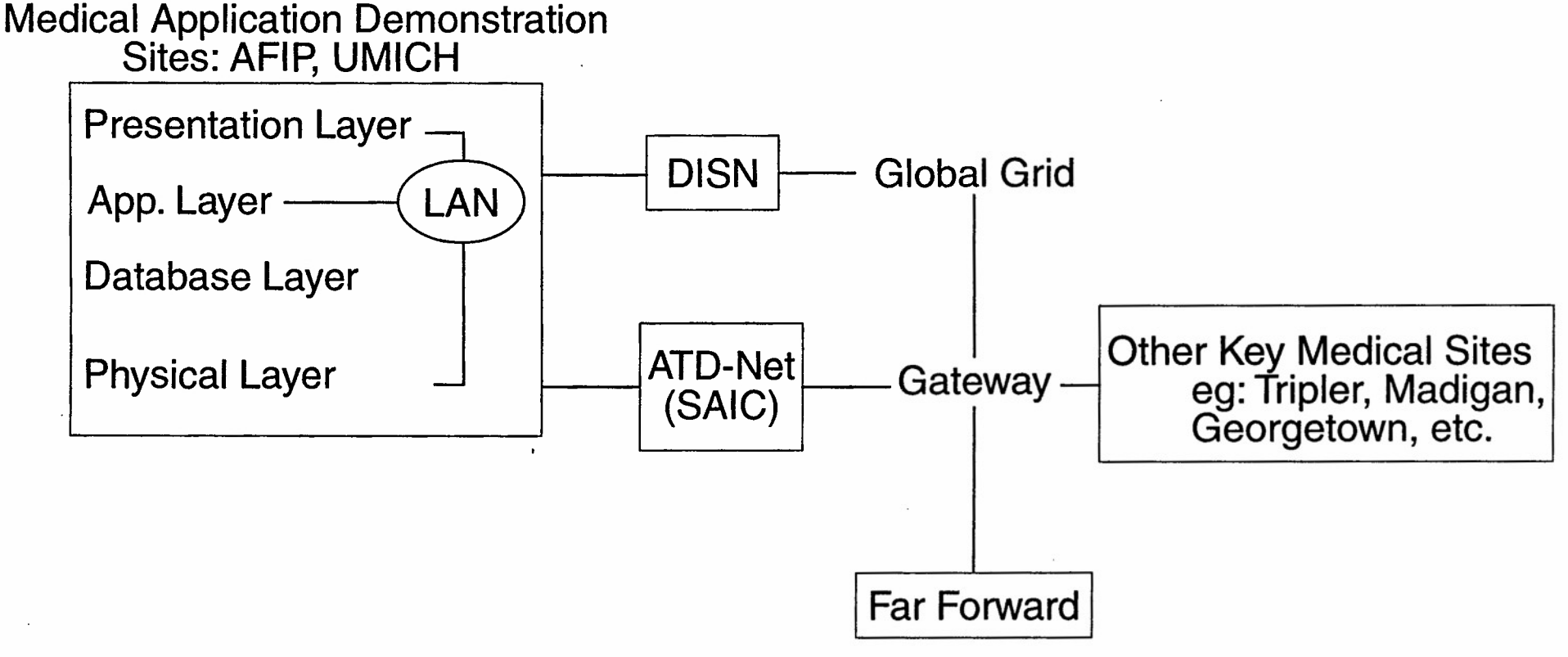
Vector Research, Inc.
~Military Insertion/Final Report

~ATD/ATM Networking

Kensall Corporation
~DARPA Telepathology Hardware

A3

Pathology Technology Insertion into the DOD-Wide Medical Network: Proposed Coordinator - Vector Research, Inc. (Ann Arbor, MI)



A4

FY 1997 Program Related to the Emerging Model for DoD Medical Informatics Infrastructure

Loosely coupled Layers		FY 1997 Program	
Presentation Layer		✓	Secure Netscape Front-End Integration
Application Layer	COTS/GOTS/Custom →	✓	Affordable/Portable Mass Image/Record Storage
Database... distributed across medical delivery system		✓	Interactive Update/Simple/ Automatic
Physical Layer		✓	ATM Integration - Device & Network

Brian D. Athey, PhD

A5

Advantages and Features of UMICH-DARPA FY 1997 ATM Pathology Demonstration

~WRAMC/AFIP ATM insertion
~Scalable OC-3 implementation
~Store/Forward *and* Interactive service
~Affordable and portable local image/record storage
~Deployable into far-forward FY 1997

~Qualified/Motivated/Positioned Team
~Leverages for funded DOD programs
~Delivers/Completes two DARPA telepathology efforts

The University of Michigan Medical Center
Department of Pathology

A6

Digital Imaging Initiatives in Pathology Informatics: 1996-1998

Laboratory/Clinical Information Systems

Blood
Fluid
Gas

1996 → 1998

Surgical/Anatomical Pathology Digital Imaging

LM
↑ DIGITAL ↓
EM

Histological
Cryo/Frozen sections
Paraffin
Fixed/Embedded
Immunological

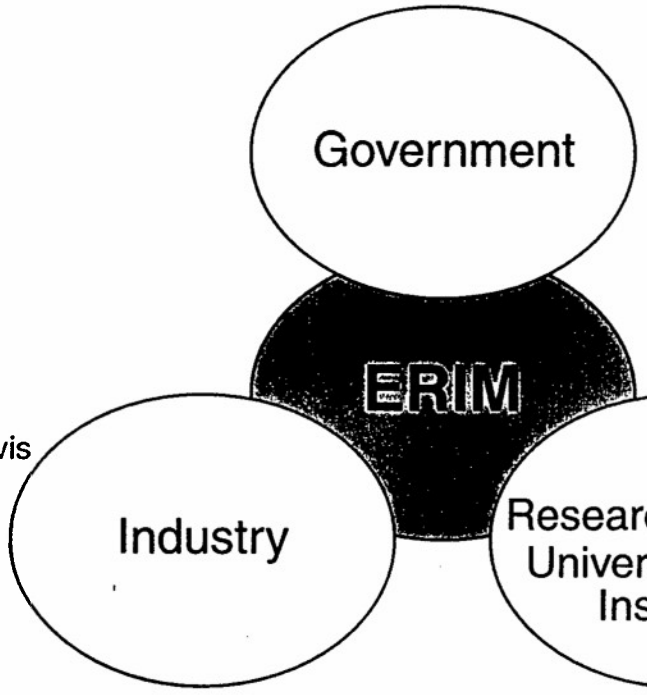
A7

Strategic Advantages of Continued UMICH/DARPA Partnership

~Succesful project demonstration and completion in FY 1997
~Field demonstrations in FY 1997 entirely possible
~Very strong Ann Arbor-based technology leveraging
~Growing partnership in pathology informatics with U Pittsburgh addresses AFIP deficiencies
~Leading digital imaging center provides basis for leadership in bio-nanotechnology
~Ground floor opportunity for tech transfer from new UMICH biomedical informatics program with strong pathology component
~Positive potential for expanded and secure UMICH/ERIM BWD participation

A8

Past and Current ERIM Imaging Patnerships in the Biomedical/Pharmaceutical Industry



~Defense Advanced Research Projects Agency (DARPA)
~Department of Energy (DOE)
~National Aeronautics and Space Administration (NASA)
~National Institutes of Health (NIH)
~National Science Foundation (NSF)

~Hoffmann-LaRoche
~Warner Lambert/Parke Davis
~Eli Lilly

~Zymark
~Meridian Instruments

~Hewlett Packard (HP)
~Eastman Kodak

~The University of Michigan Medical School
~Georgetown University
~Henry Ford Hospitals
~Armed Forces Institute of Pathology (AFIP)

A9

Open Questions

~Propose/no propose?
~Suitable contract vehicle?
UMICH FY 1997 MOD, SAIC open vehicle, or Other Transactions contract?

Proposed Next Steps

~Small ($15k) FY 1996 extension to produce five minute video with Gerard Gibbons (Visual Eyes, Inc.) for delivery August 15, 1996
~Rough cut FY 1997 cost estimate by August 1, 1996
~FY 1997 contract extension/modification proposal submitted early September, 1996

Proposed Grant Modifications to ARPA BAA-94-14

Grant # DAMD17-94-J-4512

Research To Be Conducted For

ADVANCED RESEARCH PROJECTS AGENCY (ARPA)
Defense Sciences Office (DSO)
Advanced Biomedical Technology Program (ABTP)
Richard Satava, M.D., FACS
Program Manager
3701 North Fairfax Drive
Arlington, VA 22203

TITLE OF PROPOSAL: "Development and Demonstration of a Networked Telepathology 3-D Imaging, Databasing, and Communications System: Phase II"

PROJECT PERIOD: 1 May 1996 to 31 September 1997

AMOUNT REQUESTED: Task 1: FY 1996: $529,938
Task 1: FY 1997: $552,481
Tasks 2 and 3: FY 1997: $1,563,532

PRINCIPAL INVESTIGATOR: Brian D. Athey, Ph.D.
Assistant Professor
Department of Anatomy and Cell Biology
The University of Michigan Medical School
Ann Arbor, MI 48109-0616
313-763-6150

OFFICER TO WHOM AWARD DOCUMENTS SHOULD BE MAILED:
Neil D. Gerl, Ph.D.
Project Representative
Division of Research Development and Administration
The University of Michigan
3003 South State, Room 1058
Ann Arbor, MI 48109-1274
313-763-6438

Signature: _____
Principal Investigator

Abstract

Three grant modification program tasks for the remainder of FY 1996 and for FY 1997 are being submitted to ARPA for evaluation to increase funding of the existing grant "Development and Demonstration of a Networked Telepathology 3-D Imaging, Databasing, and Communications System: Phase I (DAMD17-94-J-4512)" awarded to Dr. Brian D. Athey at the University of Michigan (UMICH) Medical School. The system concept for this grant modification is shown in Figures 1 and 2 below.

Task #1--FYs 1996/1997: Pathology Applications Software. Our team will provide to ARPA visualizations of two processed high resolution digital color microscope pathology image data sets and a demonstration of a pathology-specific image understanding application. In generating the demonstrations, ERIM will develop software tools as necessary for color 2-D and 3-D image restoration, color image processing, segmentation, interactive virtual slide navigation and display, and visualization. A video tape of these processed 3-D datasets, including an explanation of the image content and the techniques used to produce them, will be delivered by ERIM to UMICH, who will then deliver them to ARPA. Additionally, ERIM will develop a pathology-specific image processing application such as cell counting and will produce a video tape demonstration. During software development and testing, ERIM will consult with UMICH pathologist Dr. Kent Johnson andd AFIP Pathologist, Dr. Robert Becker. The video tapes will illustrate to ARPA the best available in 2-D and 3-D digital pathology imaging, 5-10 years ahead of the pathology marketplace. The data sets for this task will be collected by the UMICH team using equipment already developed and tested in this program. At the end of FY 1997 ERIM will deliver software developed under this task to UMICH and to AFIP.

Task #2-- FY 1997: Digital Pathology Interactive Microscope (DPIM). This modification will provide for the completed design, prototyping, and testing of a remote-controlled high resolution digital Telepathology system developed specifically for reference laboratories and tertiary care centers, such as the Armed Forces Institute of Pathology (AFIP) and the University of Michigan Medical Center (UMMC). This system has been named the "Digital Pathology Interactive Microscope" (DPIM), and is described

in detail in a Technical Proposal and Statement of Work (SOW) developed by the medical imaging team at the Environmental Research Institute of Michigan (ERIM). If funded, ERIM would be awarded a subcontract from UMICH to design, build, and deliver these units if this proposed modification is funded. The software and integration work performed will enable economical and compatible compact prototypes of far-forward and field deployable units to be rapidly designed, produced, and placed. During FY 1997 delivery and testing of the DPIM will take place at UMICH. Thi unit will be capable of remote operation through ISDN and OC-3 ATM service. Video tape reports on DPIM will be presented to ARPA at the end of and FY1997.

Task #3-- FY 1997: Networking Demonstrations. This modification will provide a full complement of tests demonstrating the Local Area Network (LAN) and Wide Area Networking (WAN) capabilities of the ISDN and ATM functionality of DPIM. This will include an ATM OC-3 network demonstration of DPIM remote control, high resolution color digital image capture, DICOM compliant image databasing, remote image retrieval, and interactive consultation between UMICH and AFIP. This will take place using the ARPA ATD network, accessing the Capitol Region at the Naval Research Laboratory (NRL) site managed by Dr. Hank Dardy. Given the central importance of successful ATM networking activities to military medicine, Dr. Athey will update ARPA quarterly on progress.

For all these three tasks, ERIM will be primarily responsible for coordinating with participating commercial organizations such as Nikon, Inc., FORE Systems, Hewlett-Packard Federal, and Eastman Kodak Digital Science.

System Concept Viewgraphs (Figures 1-3)

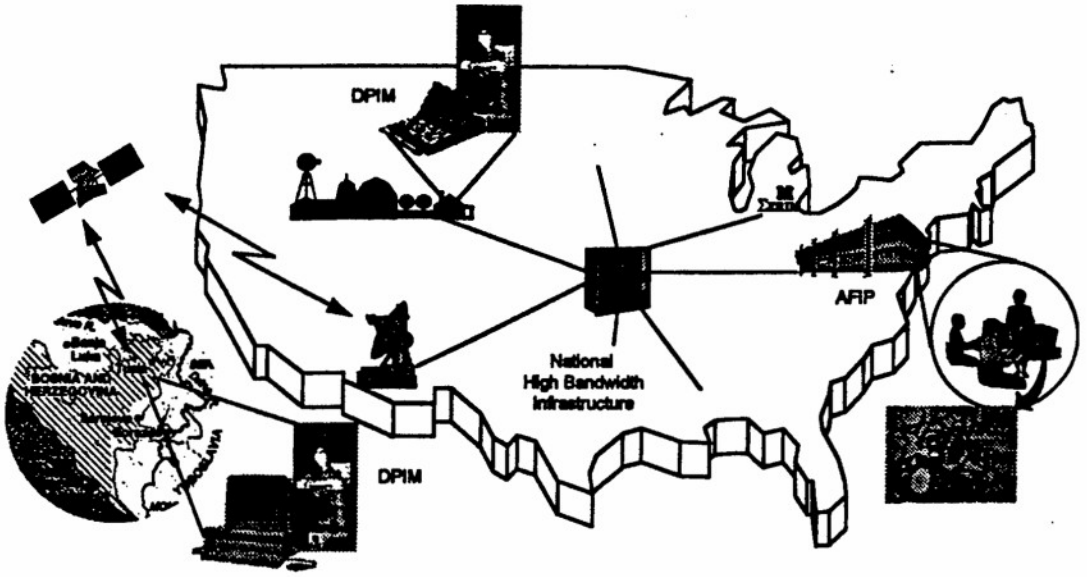


Figure 1. System Concept For The Fully Deployed DPIM

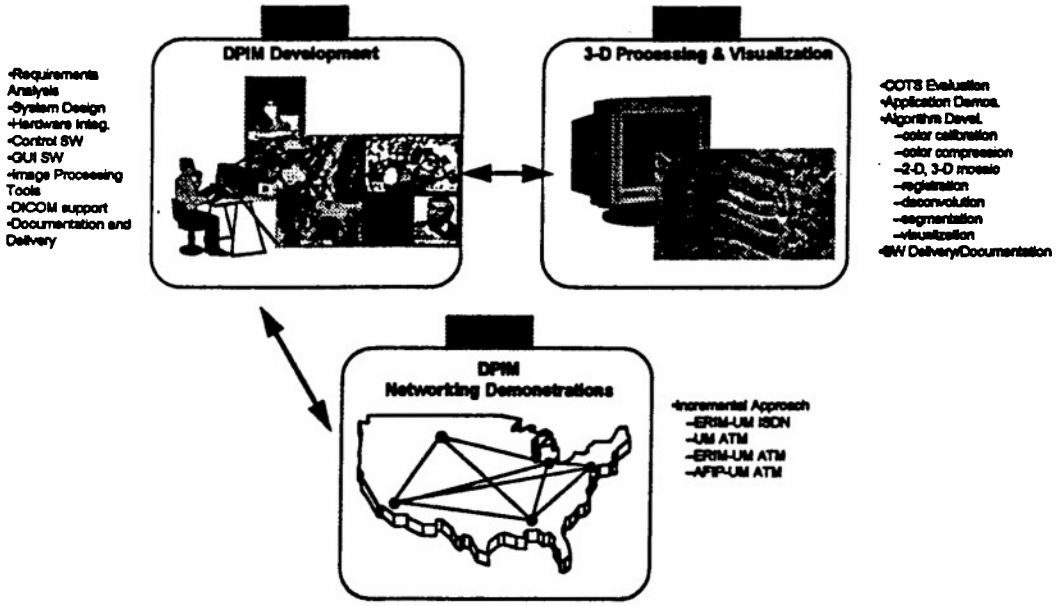


Figure 2. Relationships Between Three Tasks In Proposed Grant Modification Defense Relevance

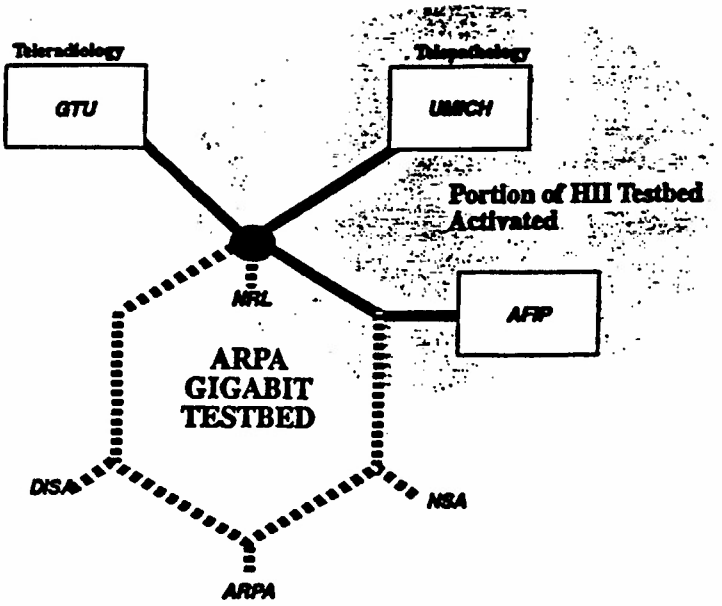


Figure 3. Diagram of Proposed Networking Activity in the Context of the ARPA ATD Net

Defense Relevance

It is well recognized that a successful and broad implementation of Telepathology services in the military (and civilian) medical system is dangerously behind the radiology world from almost all points of view, from sensors to Picture Archiving and Communications Systems (PACS). Military pathology is especially vulnerable, owing to the limited and dwindling number of pathologists currently employed by DoD. Continued development and delivery of interoperable and standards-based digital pathology systems at the cutting edge of digital imaging, computer, and communications technology is the focus of these proposed grant modifications. These systems will address the need for a distributed system to deliver pathology service independent of the constraints of time and physical location.

Task #1: The University of Michigan/ERIM/AFIP team, with ARPA's support and encouragement, is committed to pushing the state of the art in pathology imaging and image handling. The 2-D and 3-D imaging software development and demonstration projects chosen represent a broad overview of digital color imaging for pathology, present and future--again with the goal of moving pathology imaging and image management into the 21st century. These demonstrations will define what is now possible and needed to achieve this goal, and to make these technologies broadly accessible throughout the military medical system by their use and refinement at AFIP.

Task #2: There is currently no commercially available integrated microscope system to allow for the field deployment of a reference grade pathology system which can assist medics, and can be operated remotely and interactively using ATM and ISDN communication methodologies. The proposed DPIM will set a "gold standard" for development of such systems in military medicine by providing the resolution and number of ages to the pathology expert to insure accurate diagnosis. This will be achieved by a three-way development partnership involving UMICH, ERIM, and AFIP. The system will provide a development platform and prototype system to allow for a rapid introduction of this needed technology into the far-forward, hospital ships and submarines, and other remotely accessible areas. Compatibility with the emerging military medical communication network will continue to be specifically addressed in this program.

Task #3: ISDN and ATM networking functionality, including highly interactive and remote capabilities of devices such as DPIM, are critical for all future delivery of primary and secondary diagnostic grade military pathology digital imaging, as well as military forensics digital imaging. Systems such as DPIM will allow for critical battlefield and remote consultation, as well as the sharing and redistribution of pathology-relate work across the military medical system internationally as need arises. Networking demonstrations to be provided in this task will set a baseline to assess the usability of these networking methodologies for pathology. Complete specification, procurement, and testing of this networking technology using a DPIM installed at UMICH, and a H-P 770 workstation at AFIP will be provided in this task. This team will work with Dr. Silva at ARPA to connect Dr. Becker's laboratory at AFIP to the ARPA-funded ATD net. MCI will provide OC-3 service from UMICH to NRL. To insure ease of ATM compatibility throughout the development and demonstration phase, FORE Systems ATM equipment will be used throughout, under the guidance of Dr. Dardy at NRL.

Relationships and Improved Interfaces Compared to the Current Program

This proposed grant modification is a continuation of the existing program and builds on its efforts in several ways. Most importantly, it transfers the responsibilities for the production of prototypes, software, and deliverables to ERIM, an organization with a long

history of timely and efficient delivery of imaging technology for a wide range of government and private sponsors, including ARPA. This frees the UMICH component of this grant to be exclusively focused on its strengths in this program, which are providing a medical imaging and networking testbed. Additionally, the PI has determined that ERIM provides a more appropriate interface with the military than UMICH, and that ERIM has more qualifications to provide timely deliverables than UMICH. AFIP is directly included in this grant modification, insuring that the best military pathology testbed available internationally is using the technology provided, and will help to modify the working prototype after it is rolled out of the imaging laboratory. For all these three tasks, ERIM will be primarily responsible for the coordinating with participating commercial organizations such as Nikon, FORE Systems, Hewlett-Packard Federal, and Eastman Kodak Digital Science.

Progress in Phase I

Progress was made on all aspects of BAA 94-14 in FY95. These include workstation choice and procurement, digital camera procurement, pathology specific software and database evaluation, assessment of optical archiving technology, and ATM networking. Specific recommendations have been made to Drs. Satava, Jenkins, and Jones to expand the scope of the program, leading to providing successful delivery of technology and ATD with NRL and AFIP. A brief description of critical technology elements follows: 1) Workstation: Identification of H-P 770 series workstations for Reference Telepathology applications has been made. H-P will donate two of these to the program in FY96. H-P 715, 735, and 755 were evaluated and determined to have limited I/O capability for ATM applications; 2) Database: The Versant object-oriented database management system has been chosen. This was tested by ERIM on another contract, utilizing results obtained during Hoffmann-LaRoche production pathology imaging performed at UMICH. Versant works well and is easy to use; 3) Pathology Image Analysis SW: Work has been done with ERIM to evaluate the NOESIS Vision Visilog development package for pathology-specific applications development. Visilog has 24-bit color processing capability and an easy-to-use Graphical User Interface; 4) Digital Camera: Kodak contributed a 1000 x

1500 line 36-bit Color DCS-420 to the program in FY95. Color calibration and increased frame acquisition speed is needed. This camera will work for remote applications where pathology still imagery is acceptable; however, further evaluation of suitable cameras is on-going; 5) 3-D Microscope: In FY95 a standard laboratory brightfield microscope was used. The Meridian Ultima 570c UV/VIS scanning stage Laser Scanning Confocal Microscope (LSCM) was delivered into the program during February 1996, allowing for image production needed for work in Task #1 and for providing a prototyping platform for production of the DPIM; 6) ATM Networking: Fore Systems ATM equipment was evaluated for use in pathology LANs and ATD purposes. The LAX-20 product did not provide consistent service to mux ethernet, FDDI, and ATM services, and cannot be used reliably as a router. The ASX-200 ATM switch has been tested. It was found to be reliable. It is proposed that a next generation ASX-200 product be procured in the beginning of FY 1997; 7) Voice Recognition, Data Dictionary: Based on meetings with Kurzweil corporate officials, it is suggested that a Kurzweil AI pathology voice recognition system be purchased and tested in this expanded program. In addition, Dr. Athey has been consulting with Dr. Paul Clayton, medical informatics head of the Columbia University College of Physicians and Surgeons. He will assist the team in identifying the NLM compatible meta-language dictionary to be used in the final DPIM; 8) Optical Storage Technology: A 3/4 TB Kodak ADL 2000 near-line optical storage device was installed and tested using the Unitree+ data management software. This SW was unusable for pathology applications. The Multistore 3.0 Hierarchical Data Management system, provided by the Eastman Kodak Company, will be implemented FY 1996 as a replacement. This will give the best available storage solution for the images generated during the remainder of the program, and the best follow-on potential for future work with NRL. The integration of Kodak Photo-CD technology to the H-P platform is still being pursued; and 9) Scaleable Compute Technology: The H-P 770 workstation was chosen to be compatible with the H-P/Convex platform, which was tested in another project; 10) Nikon has been identified as the likely commercial partner for DPIM development and software commercialization.

Technical Barriers and Deficiencies Identified in Phase I

During Phase 1 many technical barriers and deficiencies in our initial design concept were identified, to a large extent owing to numerous discussions with Dr. Becker and colleagues at AFIP. The most important being an inadequate plan to navigate the specimen using a digital "virtual glass slide". These include a lack of remote operation capability on the microscope, inadequate color calibration and data compression specification, lack of low and midlevel hardware/software integration, networking protocols, immature ATM components supplied by FORE Systems, and limited interoperability with TCIMS and DICOM. Dr. Dardy has been central in helping with the ATM networking. In addition, numerous software deficiencies were identified, listed as follows: deconvolution of 3-D color image data, segmentation, 2-D and 3-D image mosaicking, microscope specific 24-bit visualization software, and pathology specific application software. This proposal addresses all these deficiencies.

Brief Description of Technical Elements in Proposed Modification

Task #1: Software development thrusts will include pathology specific applications, 2-D mosaicking, 2-D and 3-D feature extraction, 3-D image restoration, and 3-D visualization. These software elements are not currently available on commercially available systems, and are not anticipated to be available for five to ten years.

Pathology Specific Applications Software: In order for color digital imaging methods to replace conventional glass slide methods, a "virtual glass slide" will need to be produced, providing an overview of the specimen area and of specimen location that will be easily identified on the operator screen and at a remote location. This will allow the pathologist and medic, in separate locations, to be able to interactively "navigate" the specimen. This application will be developed using 24-bit color imagery obtained at UMICH in Dr. Athey's laboratory. Dr. Johnson of UMICH Pathology Department will work with Dr. Harmon on applications of the virtual slide capability to renal biopsy image handling and clinical image processing. Drs. Harmon and Johnson will consult with Dr. Becker at AFIP regarding these pathology-specific applications.

3-D Software Development and Demonstration: In this project, two 3-D digital color microscopic biomedical image data sets will be collected by UMICH personnel, processed by ERIM personnel and a video produced and delivered to UMICH and then on to Dr. Satava at ARPA. Two 3-D data sets to be produced are as follows: 1) A triple-label 3-D LSCM graphical image rendering illustrating the tissue ultrastructure and each cellular location in a 3-D section of the Organ of Corti (inner ear). This object has been chosen as it is considered to be the most complex of all biological tissues. This will demonstrate the capability of the Meridian Instruments Ultima 570c Laser Scanning Confocal Microscope (LSCM), partially funded by ARPA in Phase 1; and 2) A 3-D data set will be produced from a serially-sectioned, histologically-stained temporal bone data set obtained from the AFIP Developmental Anatomy collection. These sections will be selected by Dr. Athey, Professor Hawkins (UMICH), Dr. Jones (ARPA), and Dr. Noe (AFIP). The images will be digitized at AFIP, using an in-house slide digitization apparatus by Mr. Walter Meixner and transported to Ann Arbor for 3-D processing. These efforts leverage Dr. Athey's ASSERT Contract DAAH04-95-1-04151.

Task #2: The Digital Pathology Interactive Microscope (DPIM) will have the ability to "store and forward" color-calibrated and compressed 24-bit imagery with a nominal pixel resolution of 1500 x 1000 lines to a remote workstation. Frame rates for the digital image acquisition will be <500 msec, and software will also be included for fast non-quantitative viewing for focusing and scanning. The Graphical User Interface (GUI) will be intuitive and easy to use, and will allow for voice and video interaction between the pathologist and the medic. The microscope will be fully remote controlled, providing an overview of the specimen area and of specimen location, that can be easily identified on the operator screen and at a remote location. This will allow the pathologist and medic, in separate locations, to be able to interactively "navigate" the specimen. A basic microscopic image analysis software package will be included. Networking and communication will be ATM and ISDN compliant, and interact with Dr. Silva's TCIMS package. A DICOM messaging protocol extension will be configured into the sending and receiving workstation. The images produced will be accessible locally or remotely with a search engine which will be

configured with appropriate data dictionaries (e.g., UMLS and SNOMED). Because of its central importance in digital pathology service, the Kurzweil AI pathology voice recognition system will be installed onto a pathology workstation to allow for remote ISDN network demonstration in FY 1997.

Task #3: The ultimate goal of this task will be to provide a working demonstration of door-to-door ISDN and ATM Telepathology service from UMICH to AFIP via NRL, using DPIM. To achieve that goal by the end of FY 1997, continuous testing of the functionality of the components across the network will be addressed. This will be coordinated out of UMICH. An incremental approach to the development, implementation, integration, testing, and evaluation of networking capabilities will be taken. Steps will include 1) UMICH-to-ERIM ISDN link using PAX-IT systems; 2) UMICH-to-ERIM ISDN using workstation and DPIM; 3) UMICH ATM LAN using workstation and DPIM; 4) UMICH-to-ERIM ATM WAN using workstation and DPIM; and 5) AFIP-to-UMICH ATM WAN using workstation and DPIM.

Proposed Duration of the Program: 2 years; FY 1996 (starting April-June) and FY 1997.

Hardware and Software Deliverables, Demonstrations, and Timeline (Main Milestones, see attached Technical Proposal for Specifics):

A complete chart of deliverables and timelines for all three proposed optional modification tasks in the program is seen below in Figure 4. Some specific guidelines are mentioned below.

Task #1: Data for this software development task will be collected by Dr. Athey's staff at the University of Michigan Medical School and delivered to ERIM for processing. At the end of the software development period, ERIM will deliver a video to UMICH demonstrating the capability of the specified working software modules. In addition, ERIM will deliver software developed during this task to UMICH and to AFIP. Pathology software loaded unto an H-P VFE 770 workstation will also be made available to Dr. Johnson in FY 1997.

Tasks #2 and #3: The DPIM will be designed, built, and tested at ERIM during the first 9 months of FY 1997. It will be delivered to Dr. Athey's laboratory for continued use throughout the testing and demonstration phase.

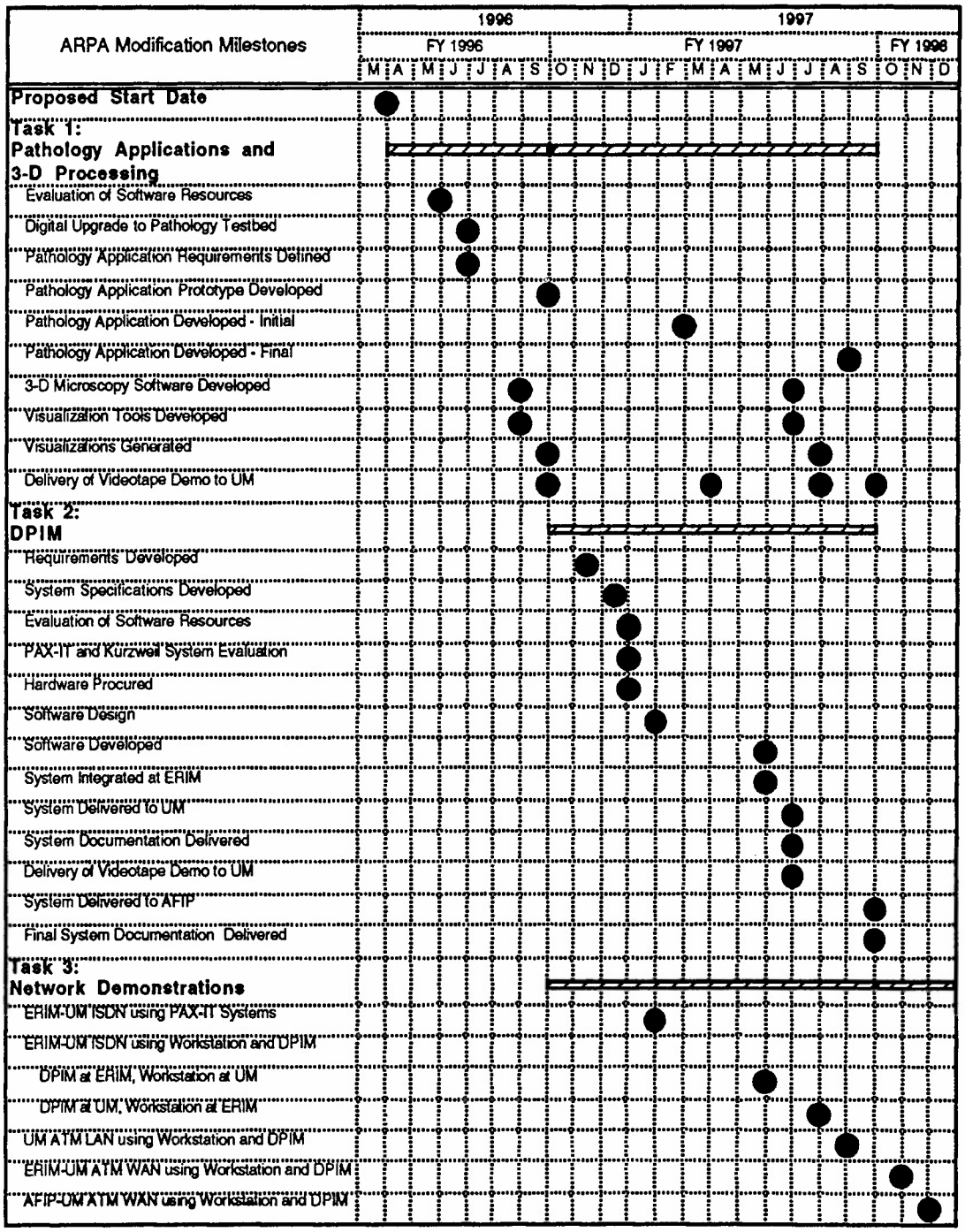


Figure 4. Gant Chart Giving Hardware, Software and Networking Demonstration Timelines

Subcontracts:

This grant modification will contain one substantial subcontracting element, which will be granted by the UMICH to the Environmental Research Institute of Michigan (ERIM) if these proposed modifications are awarded. Upon award, ERIM will submit a technical proposal giving a detailed description of the Statement of Work (SOW) and cost breakdown for ERIM's role in each of the three proposed tasks. ERIM has been identified by the PI as the best potential subcontractor based on several criteria. These include experience with pathology imaging systems and software development, excellent performance of the Hoffmann-LaRoche nerve biopsy project, and strong corporate commitment to developing pathology imaging systems and solutions.

Cost Sharing:

Hewlett-Packard Federal has donated two multiprocessor 770 workstations specified specifically for the Telepathology application to this effort. One workstation will be used for software development and will reside at ERIM. The other workstation will be delivered to UMICH Pathology Department during FY 97 as part of Task 1. Dr. Athey is also beginning discussions with Nikon relating to cost sharing in FY 1997 on Tasks 2 and 3.

Performance Locations

Task 1 software development and video documentation will be performed at ERIM. The software will be tested by the UMICH team at UMICH. For Task 2, the DPIM will be designed, specified, built, and preliminarily tested at ERIM. ISDN capability will be tested between UMICH and ERIM. The unit will then be moved to Dr. Athey's laboratory for ISDN and ATM networking tests and evaluation, with UMICH coordinating and managing these tests. Primary development of networking capabilities under Task #3 will take place at UMICH. ERIM will be used as a second location for development and testing of WAN network capabilities. These activities will be coordinated with the DPIM development work under Task 2.

Intellectual Property Provisions:

This project will be a joint development effort between the University of Michigan and the Environmental Research Institute of Michigan (ERIM), who will jointly negotiate IP provisions. This team will license to AFIP full access and use of hardware and software technology developed in this program. All hardware and software will also be available for unrestricted research, development, and educational purposes to the University of Michigan Medical School and to ERIM.

Future Commercialization Plan:

This plan will be developed with Nikon being considered as the potential lead commercialization partner. This will insure continued development of DPIM and related software. Other potential partnership arrangements are also being considered.

Budget

The budget below gives cost breakdowns for work performed in Dr. Athey's laboratory and for the proposed subcontract to be performed in Dr. Harmon's laboratory, given on a task by task basis. Budget justification for work done in Dr. Athey's laboratory will be given below. Dr. Harmon will justify ERIM'S cost at the time of grant modification approval.

a. Salaries (Incl. FB):

Table 1: FY 1996 University of Michigan Employee Salary Schedule

Name and Job Title Base Annual Salary	Monthly Salary w/ FB*	Number of Months	% of Time on Project	Total
Mr. Gene Hsu Application Visualization Specialist $25,000	$2,666	5	100%	$13,333

* Fringe Benefit rate is 28% of Base Salary

b. **Equipment:** $25K
- 50 GB Hard Disks and Controllers: $25K

c. **Software:** $29.5K
- AVS single user floating licenses: $5K
- Versant OODBMS 1 developer, 1 users: $12K
- Noesis Vision Visilog: 1 developer (including 24-bit color analysis modules): $12.5K

d. **Supplies and Materials:** $2K
- Office supplies, postage, phones, Xerox: $2K

e. **Travel, Symposiums:**

Table 2: Travel Required for Project, FY 1996

Meeting*	Location	# of Days	Airfare	Per diem Costs*
ARPA Tech, May 1996	Atlanta, GA	4	$873.00	$175.00
Image 1996	Phoenix, AZ	4	$920.00	$150.00
4 Trips to AFIP/ARPA	Washington, DC	2.5	$794.00	$200.00

*Includes meeting registration fees, transportation, lodging, and meals.

Total Travel: $9,169

g. **Indirect Costs**

The indirect cost rate at the University of Michigan is 52%. This is applied to the Base + Fringe Benefit amount of $13,330 for the Visualization Specialist. It also applies to $2K allocated to Materials and Supplies, and the $9,169 travel budget. In addition, a one-time only UMICH subcontracting fee of $5.2K has been included.

0.52 x $24,499 + $5,200 = $17,939

UMICH Task 1 Subtotal FY 1996 (a-f): $96,938

ERIM Subcontract Task 1 (see Cost Summary below and attached Technical Proposal) = $433,000

TOTAL AMOUNT UM FY 1996: $529,938

a. **Salaries:** $165,884 (Tasks 1 through 3).

Table 3: FY 1997 University of Michigan Employee Salary Schedule

Name and Job Title Base Annual Salary	Monthly Salary w/ FB*	Number of Months	% of Time on Project	Total
Brian D. Athey, Ph.D. Assistant Professor $60,000/yr. (UMICH) Tasks 1 and 3	$6,400	2	20	$12,800
TBD-Networking System Coordinator, $41,000/yr. Task 3	$4,373	12	100	$52,480
W.M. Meixner, Research Associate II $36,000/yr. Task 1	$3,840		100	$46,080
Justin Laby, $20,600/yr. Comp. Sys. Specialist I Task 1	$2,197	12	100	$26,364
Sari Failer, $22,000/yr. Research Secretary II Task 1	$2,347	12	100	$28,160
Total Salaries Task 1				$113,364
Total Salaries Task 3				$ 52,480

* Fringe Benefit rate is 28% of Base Salary

b. **Equipment:** $125K
   - Fore Systems ATM Hardware: $100K
   - Pax-It System: $25K

c. **Software:** $30K
   - Network Manager: $30K
     Tasks 2 and 3

d. **UMICH Networking Services:** $50K
   - MCI POP Ann Arbor to Med Sci II: $25K
   - Med Sci II to ERIM Clean Room (Plymouth Road): $25K
     Tasks 2 and 3

e. **Supplies and Materials:** $10K (Task 1), $10K (Tasks 2 and 3)
- Optical media, magnetic tape, cables
- Office supplies, postage, phones

f. **Travel, Symposiums:**

Table 4: Travel Required for Project, FY 1997

Meeting	Location	# of Days	Air Fare	Per diem Costs*
Medicine Meets VR V	San Diego, CA	4	$873.00	$150.00
SPIE International Symposium on Medical Imaging 10-15 Feb. 1996	Newport Beach, CA		$873.00	$150.00
Image 1997	Phoenix, AZ	4	$920.00	$150.00
8 Trips to AFIP/NRL, Washington, DC		2.5	$794	$200

*Includes room, meals, and transportation.

Total Travel: $13,345

f. **Indirect Costs**

The indirect cost rate at the University of Michigan for FY 1997 is 52.5%. This is applied to the Base + Fringe Benefit amount of $168,284K for the Staff. It also applies $75K to Networking to $20K allocated to Materials and Supplies, and the $13,345 travel budget.

(Task 1) 0.525 x $136,709 = **$71,772**

(Tasks 2 and 3) 0.525 X $112,480 = **$59,052**

UMICH Subtotal FY 1997 (Task 1) = **$208,481**

ERIM Subcontract: FY 1997 (Task 1) = **$344,000**

UMICH Total FY 1997 (Task 1) = **$552,481**

UMICH Subtotal FY 1997 (Tasks 2 and 3) = **$326,532**

ERIM Subtotal FY 1997 (Tasks 2 and 3) = **$1,237,000**

UMICH Total FY 1997 (Tasks 2 and 3) = **$1,563,352**

Budget Justification for UMICH Testbed: Dollars spent in Dr. Athey's laboratory will be used to maintain the personnel infrastructure (Budget Section a): 1) collect data for Task 1; 2) test DPIM (Task 2), and report results back to Dr. Harmon and Dr. Becker; and 3) coordinate networking tests in Task 3. A summary of ERIM costs by Task are shown below in Tables 5a and 5b.

Table 5a. ERIM Cost Summary by Task and Fiscal Year

Task	FY 96 Costs ($K)	FY 97 Costs ($K)	Total ($K)
Task 1: Pathology Applications and 3-D Processing	433	344	777
Task 1.1 COTS and GOTS Software Evaluation	25		25
Task 1.2 Pathology Applications Software	188	156	344
1.2.1 Kidney Biopsy Facilities Upgrades	85		85
1.2.2 Virtual Slide Software Development	56	60	116
1.2.3 Kidney Biopsy Applications Development	47	96	143
Task 1.3 3-D Processing and Visualization	121	141	262
1.3.1 Custom Software/Tools	21		21
1.3.2 Visualization Generation	89	123	212
1.3.3 Videotapes of Visualizations	11	18	29
Task 1.4 Software Documentation	22	10	32
Task 1.5 Development Software Purchase	40		40
Task 1.6 Pathology Consulting	27	26	53
Task 1.7 Travel	10	11	21
Task 2: DPIM System Development and Delivery		1104	1104
Task 2.1 DPIM Hardware Development		462	462
2.1.1 DPIM System Specification and Design		116	116
2.1.2 DPIM System Implementation		220	220
2.1.3 DPIM System Integration/Test and Demonstration		81	81
2.1.4 AFIP DPIM Workstation Integration and Installation		40	40
2.1.5 Travel		5	5
Task 2.2 DPIM Software Development and Integration		210	210
2.2.1 PAX-IT and Kurzweil System Evaluation		28	28
2.2.2 DPIM System Software Development		144	144
2.2.3 DPIM System Software Documentation		30	30
2.2.4 Travel		8	8
Task 2.3 UMICH DPIM System Component Purchases		301	301
2.3.1 UMICH DPIM Hardware Purchases		287	287
2.3.2 UMICH DPIM Software Purchases		14	14
Task 2.4 AFIP DPIM Workstation Component Purchases		77	77
2.4.1 AFIP DPIM Workstation Hardware Purchases		64	64
2.4.2 AFIP DPIM Software Purchases		13	13
Task 2.5 DPIM Development Software Purchases		54	54
Task 3: Network Demonstrations		133	133
Task 3.1 Demonstration Support		99	99
Task 3.2 ERIM Network Infrastructure Upgrades		31	31
Task 3.3 Travel		3	3
Total	433	1581	2014

Table 5b. Estimated Cost of Equipment in Table 5a Which will be Purchased by ERIM on Proposed Subcontract for Integration and Delivery to Umich and AFIP

	Total per Task ($K)	Description
Task 1	45	UMICH Kidney Biopsy Facility Upgrades
Task 2	301 77	UMICH DPIM AFIP DPIM Workstation
Task 3	N/A	
Total	423	

ADDENDUM--DESCRIPTION OF INSTITUTIONS AND TEAM:

The University of Michigan Medical School

The Department of Anatomy and Cell Biology (ACB) in the University of Michigan Medical School is the home of the Digital Microscopy and Scientific Visualization (DMSV) Collaboratory where the work will be done. Under the leadership of Professor B.M. Carlson MD, PhD, ACB is striving to become one of the world's leading groups in developing a cross-disciplinary team to respond to the "grand challenge" nature of visualizing macro- and microscopic human anatomy for research and educational purposes. Dr. Athey, PI of this project, is founder of the DMSV. The University of Michigan Department of Pathology, under the leadership of Dr. Peter Ward, is one of the largest and well known academic Pathology departments in the country. The University of Michigan is the only University in the nation which as a top-ten rated Medical School and Engineering College on one campus.

The Environmental Research Institute of Michigan (ERIM)

The Environmental Research Institute of Michigan (ERIM) is a nonprofit, high-technology organization that performs over $70M of imaging research and related services for both government and private sponsors annually. Since 1946, it has specialized in developing innovative sensor and image processing technologies that cover a wide range of remote sensing devices and techniques. Historically, there have been many practical application areas for ERIM's research. These include defense and intelligence systems of all kinds, environmental assessment methods, and many economic and commercial development projects. ERIM's areas of expertise include Sensor Design and Development; Image & Signal Processing; System Integration; and Industrial Defense and Technology Applications. ERIM is currently making a strong commitment to leverage these world renowned imaging technologies and expertise into the areas of biomedical imaging and visualization, broadly defined to include devices and systems, diagnostic grade imaging

software and analysis packages, as well as enabling technologies for telemedicine, including mass digital medical image data and record storage and warehousing.

Brief Resume of Key Personnel and Proposed Roles

Dr. Brian Athey (UMICH/ERIM) will be Principal Investigator. Dr. Athey is currently an Assistant Professor of Anatomy and Cell Biology at the University of Michigan Medical School. His research interests include the acquisition, processing, storage, and retrieval of 2,3, and 4-D microscopic datasets for research and clinical use. He also serves as Director of Biomedical Imaging Programs in the Executive Division of the Environmental Research Institute of Michigan (ERIM). He will be responsible for delivery of quarterly milestones and videos to ARPA. He will also coordinate the identification of project problems and solutions, and for timely delivery of promised hardware and demonstration elements to the sponsor and identified pathology application centers. Dr. Laurel Harmon (ERIM) will be ERIM subcontract Project Manager and overall technical coordinator of the projects. Dr. Harmon, who is a program manager at ERIM focusing on biomedical imaging projects, is Head of the ERIM's Symbolic Processing Department. Dr. Harmon has been working in the field of pathology imaging intensively for the past two years, and served as software development and data production supervisor on the University of Michigan's $2.5M Hoffmann-LaRoche digital EM nerve biopsy imaging project. Dr. Kent Johnson will serve as a Pathology consultant to Dr. Harmon. Dr. Johnson, currently appointed as Professor of Pathology at the University of Michigan Medical School, has been a practicing Pathologist for over 20 years. He served at AFIP with Dr. Ward, Chairman of the University of Michigan Department of Pathology, in the late 1960s. Dr. Johnson is Director of the Pathology Department's Morphology Imaging Facility. Col. Robert Becker, M.C. is Director of the Cellular Pathology Imaging Facility at AFIP. His research and conciliate interests are related specifically to color digital microscopic imaging of cells and tissues of clinicopathologic nature, with renal tissue biopsy imaging and cytonuclear imaging being specialty interests. In addition, the following University of Michigan collaborators will provide samples and guidance regarding specimens for Task 2: Dataset

1--Professor Richard Altschuler and Dr. Yoash Raphael of the Kresge Hearing Research Institute (KHRI); 2--Professor Emeritus Joseph Hawkins, KHRI.

ERIM

January 16, 1996

Technical Proposal:

Telepathology Systems Development and Demonstrations

Subcontract proposal prepared in support of proposed modifications to University of Michigan ARPA Grant No. DAMD17-94-J-4512 entitled "Development and Demonstration of a Networked Telepathology 3-D Imaging, Databasing, and Communications System: Phase II"

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1.0 Overview

1.1 Introduction

The University of Michigan Department of Anatomy and Cell Biology (UMICH), is proposing contract modifications entitled "Development and Demonstration of a Networked Telepathology 3-D Imaging, Databasing and Communications System: Phase II" to ongoing ARPA grant number DAMD17-94-J-4512. ERIM proposes here to accomplish the following tasks in support of the UMICH effort:

- develop and demonstrate an interactive, networked digital microscope and data handling system tailored for pathology applications: Digital Pathology Interactive Microscope (DPIM).
- develop and deliver 3-D visualizations and digital datasets obtained from microscopic imaging of selected intact and sectioned biological materials.
- support a series of demonstrations of the DPIM linked via high-speed networks between sites.

The tasks described here are directed toward both near- and long-term requirements of digital pathology. The long-term goal of this effort is the development of fully-integrated, full-color, networked, two- and three-dimensional digital imaging and data handling systems for pathology applications, schematically illustrated in Figure 1. The DPIM, as developed and demonstrated on this program, represents the state-of-the-art in deployable networked digital (2-D) light microscopy for telepathology applications. The development of high-resolution, high-quality 3-D visualizations and datasets of biologically relevant materials will demonstrate what will be achievable in the longer-term via 3-D imaging. The program has been structured so that the DPIM will support a smooth transition to integrated 3-D imaging and data processing in the future.

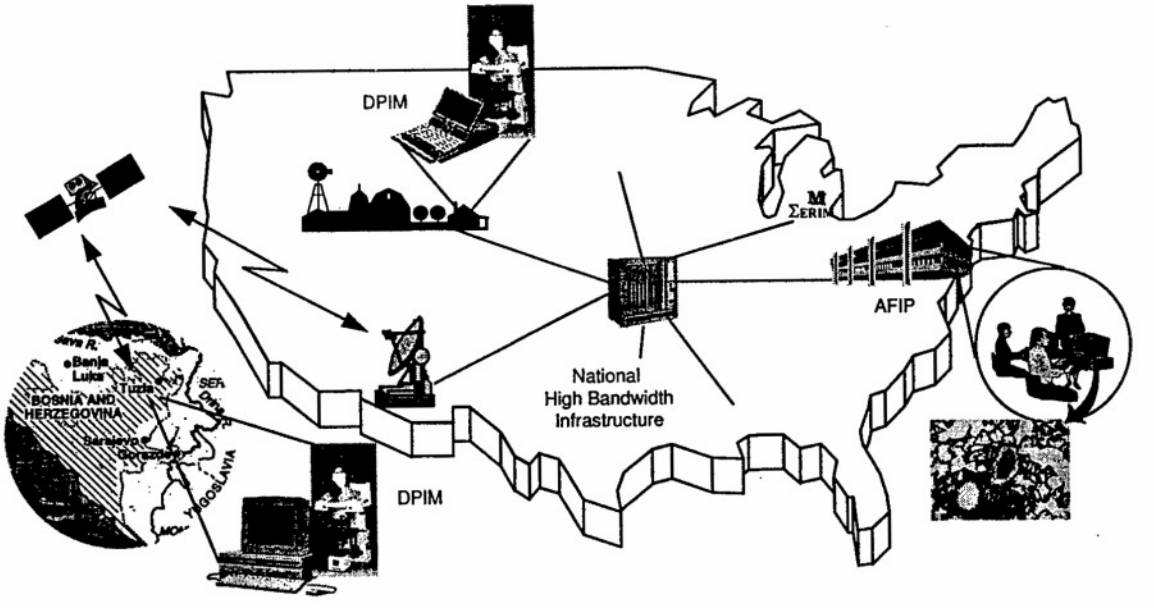


FIGURE 1. System Concept for Fully Deployed Telepathology Systems

The work proposed here represents a rare collaboration between military and civilian medical communities, academic medical centers, and the systems development and integration experience of a non-profit organization with significant history in both commercial and defense programs. ERIM's work will be performed in consultation with Col. Robert Becker, USAF MC of the Armed Forces Institute of Pathology and Dr. Kent Johnson of the University of Michigan Department of Pathology. The DPIM system and the 3-D software tools and datasets will be delivered into both civilian (University of Michigan Medical Center) and military (Armed Forces Institute of Pathology) settings. By this means, the development team and ARPA will be able to incorporate requirements from both domains into the products of the proposed program.

The proposed activities are summarized in Section 1.2, below, followed by a description of the organization of the program in Section 1.3. The individual technical tasks are described in more detail in subsequent sections of this proposal:

- Task 1: Digital Pathology Interactive Microscope (DPIM) System Development and Delivery (Section 2.0)
- Task 2: 3-D Processing and Visualization (Section 3.0)
- Task 3: Network Demonstrations (Section 4.0)

The Statement of Work and Schedule are presented in Sections 5.0 and 6.0, followed by a summary of ERIM's program costs in Section 7.0. The planned disposition of equipment and software obtained by ERIM for the purposes of the proposed program is outlined in Section 8.0. This proposal concludes with biographies of the ERIM leadership team in Section 9.0.

1.2 Summary of Proposed Activities

Figure 2 depicts at a high level the three major tasks that comprise the proposed program.

1.2.1 Task 1: Digital Pathology Interactive Microscope

Task 1 of the effort will provide for the completed design, prototyping, testing and delivery of a remote-controlled digital telepathology system (DPIM). Under this task, ERIM will be responsible for the hardware and software specification, procurement, prototype production/delivery and demonstration of the DPIM.

The product of this task is intended to resolve a serious deficiency of both commercial and custom systems to provide a field deployable reference grade pathology system. Such a system would amplify the capabilities of field medics through remote and interactive consultation with national expertise using commercial, hi-bandwidth wide area networks. The DPIM would provide a reference standard for military medicine and serve as a test bed for future spin-offs of low-cost, deployable systems. It will ultimately enable the rapid introduction of this technology into far-forward sites, hospital ships, submarines, and other remote locations.

The Digital Pathology Interactive Microscope software will provide an integrated user-friendly graphical user interface (GUI) for the DPIM system and all of its associated hardware and software. Specific capabilities will include control software for the microscope, camera, and frame grabber; integrated video conferencing; integrated image pro-

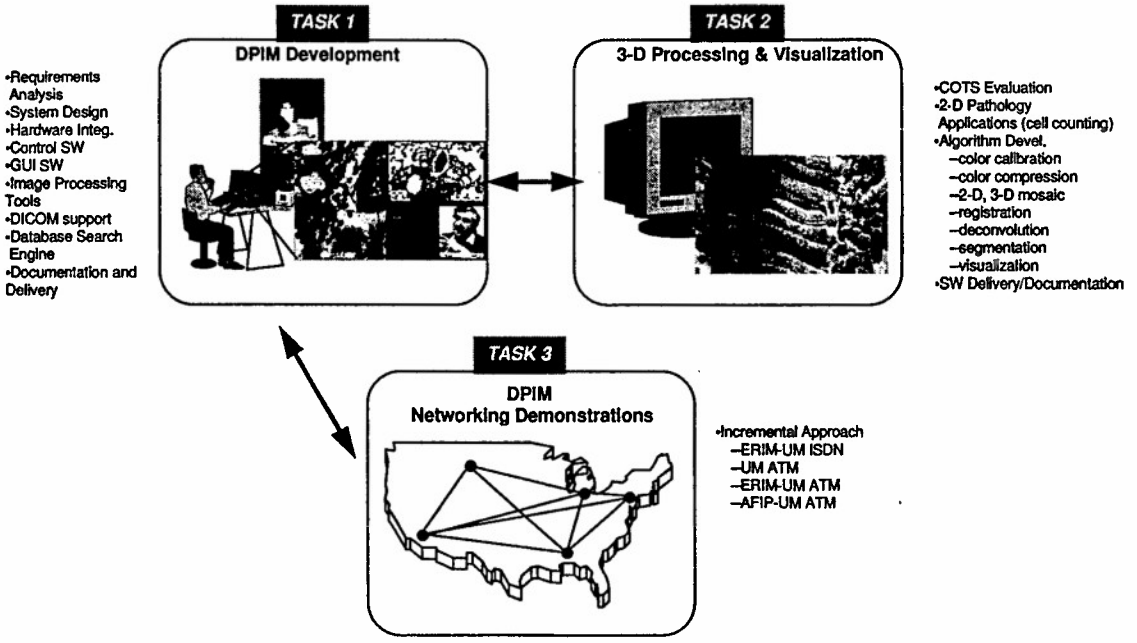


FIGURE 2. Task Structure for Proposed Program

cessing, access to an object-oriented database for the storage and retrieval of images and other data; support for DICOM standards; and support for local and wide-area high-speed networking.

In addition, a critically-relevant pathology-specific application will be developed to demonstrate the capabilities of the DPIM and the software tools. The specific application will be selected in conjunction with ARPA, the AFIP and the University of Michigan Department of Pathology. This demonstration will be videotaped and the videotape will be delivered to UMICH.

1.2.2 Task 2: 3-D Processing and Visualization

The goal of Task 2 is to demonstrate the application of state-of-the-art 3-D visualization technology as applied to pathology-specific tasks. To this end, ERIM will generate visualizations of three datasets to be provided by UMICH. These visualizations will be videotaped and the videotapes will be delivered to UMICH. Software for processing and displaying 3-D pathology data developed in the course of generating the visualizations will be delivered to UMICH and made available to the AFIP.

The three datasets identified by UMICH for use on this task are:

- A triple-label 3-D LSCM dataset of the Organ of Corti (inner ear). This object has been selected because it is the most complex of all biological tissues.
- A triple-label 3-D LSCM dataset of embedded electrodes interacting with labelled neurons and glial cells in the brain.

- A serially-sectioned, histologically stained temporal bone dataset.

1.2.3 Task 3: Networking Demonstrations

Through Task 3, ERIM will support a series of staged demonstrations of networked pathology systems. The proposed demonstrations are:

- ERIM-UMICH ISDN using PAX-IT Systems
- ERIM-UMICH ISDN using Workstation and DPIM
  - DPIM at ERIM, Workstation at UMICH
  - DPIM at UMICH, Workstation at ERIM
- UMICH ATM LAN using Workstation and DPIM
- ERIM-UMICH ATM WAN using Workstation and DPIM
- AFIP-UMICH ATM WAN using Workstation and DPIM

These demonstrations have been designed and sequenced to show the evolution of capabilities from COTS PC-based systems linked locally via readily available ISDN lines to state-of-the-art workstation-based systems linked long-distance via ATM.

1.3 Program Organization

Figure 3 shows the organizational structure of the project and the task breakdown.ERIM's program will be directed by Dr. Laurel Harmon, head of the Symbolic Processing Department in ERIM's Information and Materials Applications Laboratory (IMAL). Dr. Harmon will have primary responsibility for coordination with the University of Michigan Principal Investigator, Dr. Brian Athey, the University of Michigan Department of Anatomy and Cell Biology, and ARPA. The leadership and staff of ERIM's individual tasks will be drawn from both IMAL and the Systems Engineering and Integration Center (SEIC).

Mr. Paul Mohan, head of ERIM's Systems Engineering and Hardware Integration department in SEIC, will manage the development of the DPIM, supporting the technical leads of the two subtasks: Mr. Paul Kortesoja, DPIM hardware system development, and Dr. Alan Vayda, DPIM software development. Dr. Alan Vayda will also direct the 3D Processing and Visualization task. By combining the leadership of the two software efforts on this program, Dr. Vayda will maximize synergy between them and ensure that the program moves toward the goal of ultimately integrating two- and three-dimensional digital microscopy. Mr. Paul Kortesoja will lead ERIM's support of networking demonstrations in Task 3, reflecting the close coupling between DPIM hardware development and networking to remote sites.

ERIM's technical management team will work closely with Drs. Harmon and Athey throughout the program to ensure that the evolving system and demonstrations further the goals of the ARPA Advanced Biomedical Technology Program. Guidance will also be provided during all phases of DPIM design, implementation, testing, and demonstration through consultation with Col. Robert Becker, USAF/MC, Director of Cellular Pathology at the Armed Forces Institute of Pathology, and Dr. Kent Johnson, Professor of Pathology, the University of Michigan Department of Pathology. By this means, ARPA and the University of Michigan can be confident that the DPIM and proposed

demonstrations will meet the current and future needs of both military and civilian pathologists.

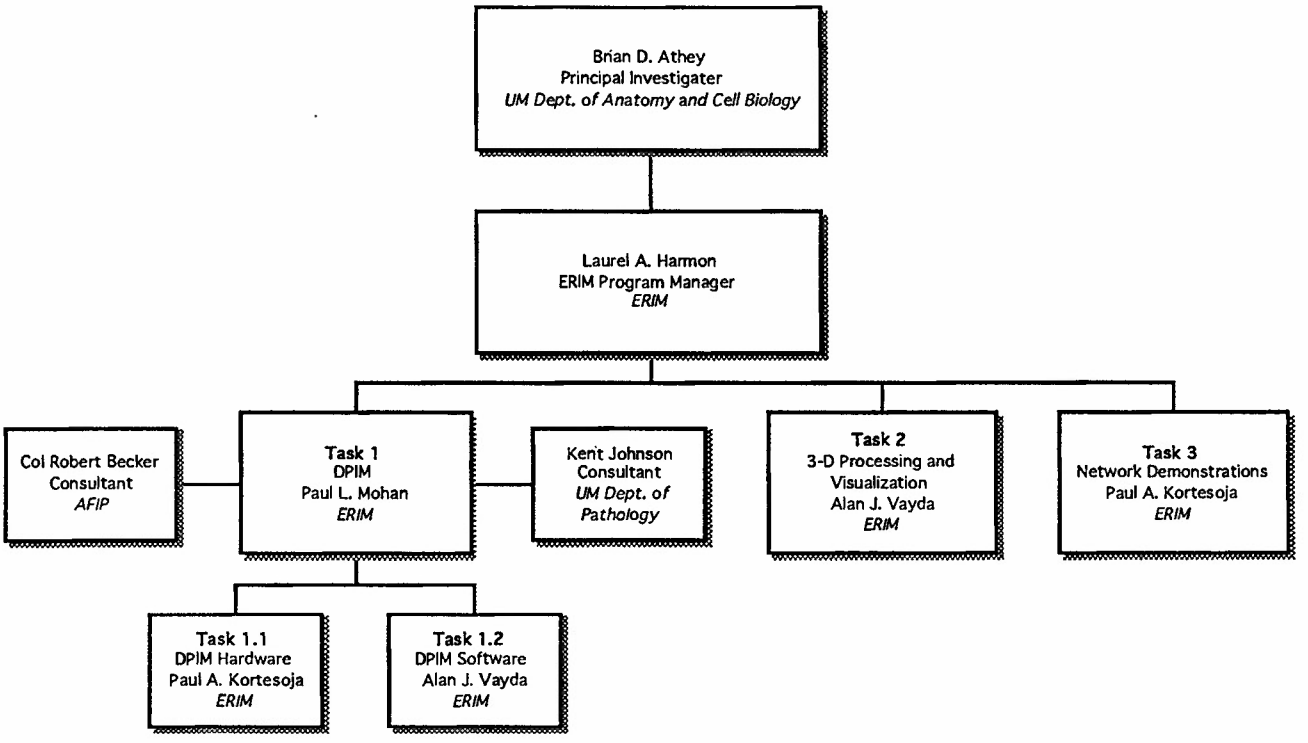


FIGURE 3. Organizational Structure and Task Breakdown

2.0 Task 1: Digital Pathology Interactive Microscope (DPIM) System Development and Delivery

2.1 Overview

Task 1 of the proposed effort will provide for the completed design, prototyping, testing and delivery of a remote-controlled digital telepathology system (DPIM). Under this task, ERIM will be responsible for the hardware and software specification, procurement, prototype production/delivery and demonstration of the DPIM.

The product of this task will resolve a serious deficiency of both commercial and custom systems to provide a field deployable reference grade pathology system. Such a system would amplify the capabilities of field medics through remote and interactive consultation with national expertise using commercial, hi-bandwidth wide area networks. The DPIM would provide a reference standard for military medicine and serve as a test bed for future spin-offs of low-cost, deployable systems. It will ultimately enable the rapid introduction of this technology into far-forward sites, hospital ships, submarines, and other remote locations. Figure 4 illustrates the DPIM concept.

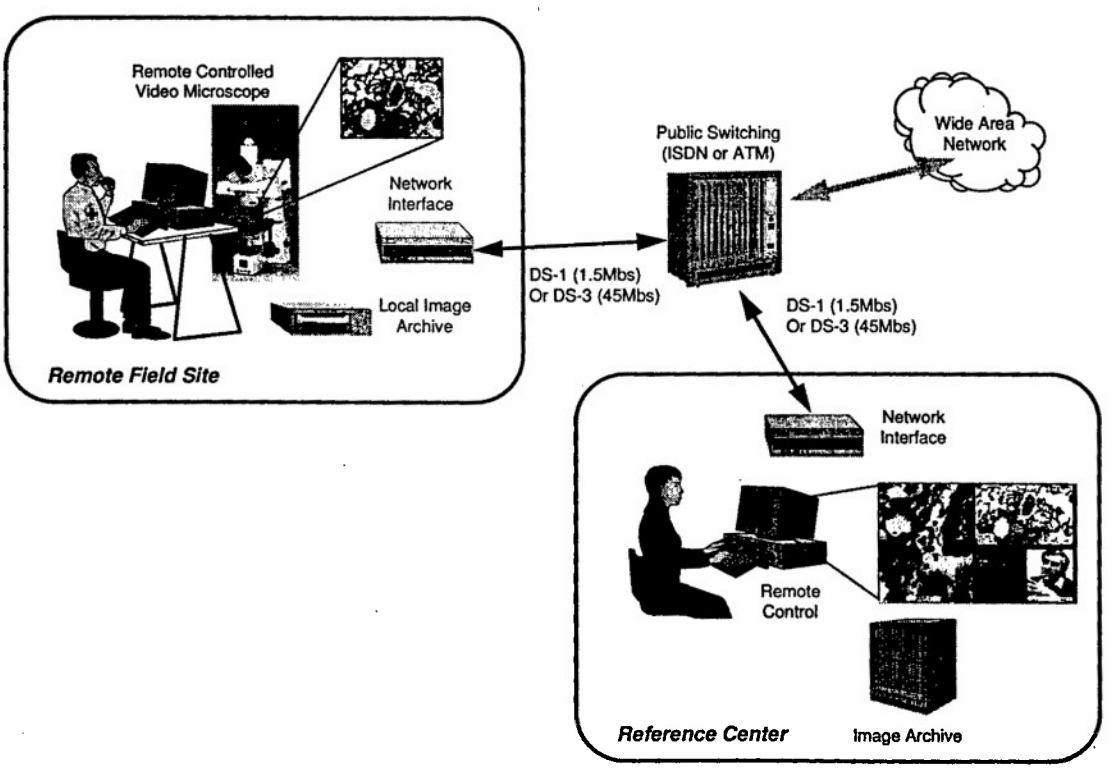


FIGURE 4. Conceptual Diagram of the DPIM

2.2 Technical Approach

A preliminary set of requirements has been established that will drive the development of the DPIM. In addition, to assure a flexible, scalable, high-performance demonstration system, further guidelines will be established in the early phases of Task 1. These requirements and guidelines are summarized in Table 1. A complete set of requirements will be identified as part of the initial DPIM hardware specification task.

TABLE 1. Preliminary Criteria for Development of the DPIM

Requirements	Guidelines
• Adhere to DICOM standard	• Apply commercial off-the-shelf components
• Interface with existing commercial inter-network standards (ATM, ISDN, etc.)	• Trade off (initially) lower-cost for higher performance
• Partner with Armed Forces Institute of Pathology to validate system architecture and develop credible demonstrations	• Highest resolution color imaging consistent with acceptable frame rates
	• Minimum interactive latency for remote microscope control and image viewing

Figure 5 shows the strawman hardware configuration for the DPIM. The two major subsystems are: 1) the user workstation and 2) the automated color digital microscope. A proposed top-level breakdown of these two subsystems is shown in Table 2. While the Olympus microscope has been proposed as a baseline instrument, discussions are ongoing with other vendors concerning automated microscopes under development which might better serve the needs of the program. The final decision will be made during the design phase of this task.

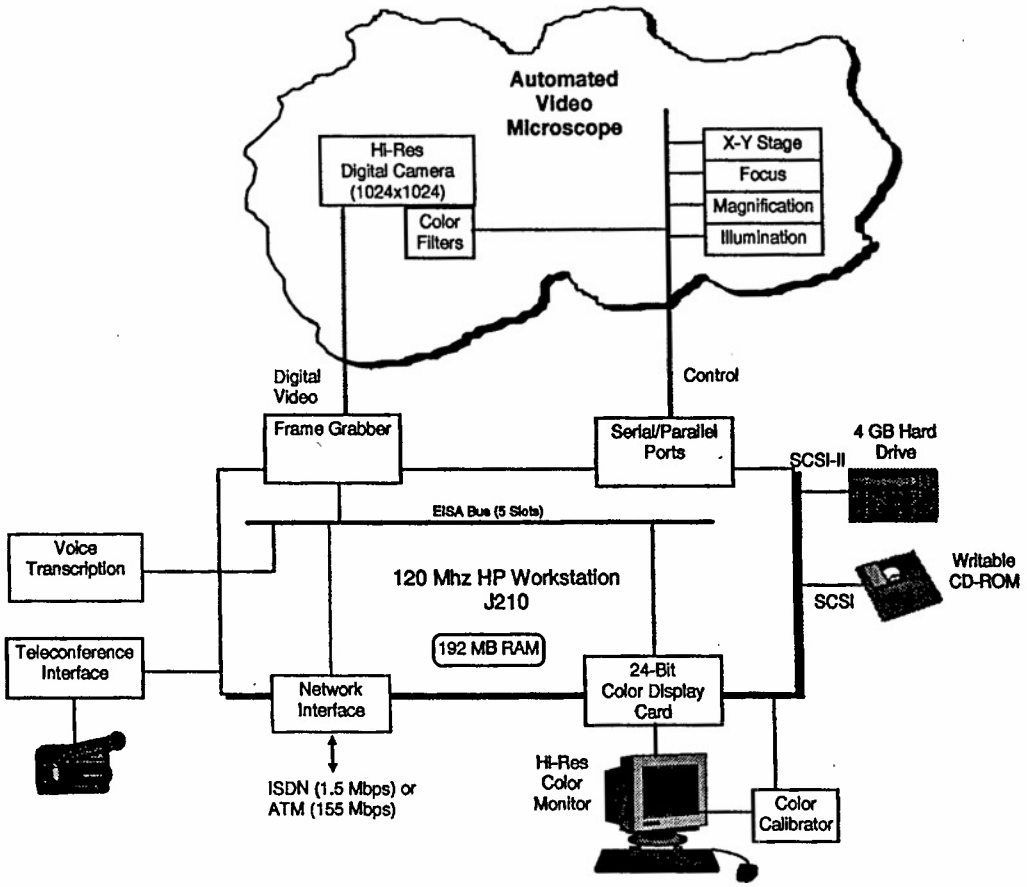


FIGURE 5. Strawman Hardware Configuration for the DPIM

TABLE 2. Top-level Breakdown of DPIM System Components

User Workstation	Automated Color Digital Microscope
• *HP J-Class Workstation Model J210* (baseline) —120 Mhz CPU w/192 Mbyte RAM —4 Gbyte Hard Drive, 1 Mbyte Read/Writable CD-ROM —1280x1024 20" color monitor —HP-UX 9.07 Operating System • *Network interface board* to support high-bandwidth link to ISDN or ATM switch • *Teleconference unit* w/ color camera and microphone • *Frame Grabber*, to support high-resolution image acquisition from the microscope camera • *Color Calibrator*, to provide active monitoring/correction of displayed colors • *Serial/Parallel Ports*, to support remote control of motorized microscope	• *Olympus AX-80 Motorized Microscope* (baseline) —Advanced research microscope for transmitted/reflected light microscopy —1.25X, 4X, 10X, 20X, 40X, and 60X objectives —Brightfield sextuple motorized nosepiece, motorized condenser, motorized stage —Multi Control Unit for motorized control —Universal Photomicrographic Unit —High-speed autofocus • *High Resolution Digital Video Camera* —≥1024 x 1024 pixel CCD array —Integrated color filter wheel w/ controller (for monochrome cameras) —24-bit RGB, frame rate ≤ 0.5 sec/frame

2.3 Task 1.1: DPIM Hardware Development

The ERIM hardware development team will be responsible for the specification, assembly, integration/test, and field support of the DPIM remote-controlled digital pathology bright field light microscope system. Hardware development activities will be closely coordinated with the ERIM software development task to ensure a unified system design. Effort under this task will encompass all necessary networking peripherals (switches, fiber, etc.) to support the DPIM. The initial system will be delivered to UMICH. Subsequent tasks will provide for duplication and installation of a DPIM at AFIP and training on its use. The DPIM hardware development effort will be executed through the following tasks:

- Task 1.1.1—System Specification and Design
- Task 1.1.2—System Implementation
- Task 1.1.3—System Integration and Testing
- Task 1.1.4—AFIP System Replication
- Task 1.1.5—On-Site Training at AFIP

A detailed breakdown for these tasks follows.

2.3.1 Task 1.1.1: DPIM System Specification and Design

Under this task, the hardware team will work with the other program task leaders and with AFIP to refine the system hardware requirements for the DPIM. Based on these requirements, a hardware system specification document will be developed to drive the

design of the operational model and to direct the specification and procurement of appropriate hardware components and subsystems. The operational system model will be developed in close collaboration with Dr. Kent Johnson to insure maximum utility and "user friendliness" of the end system. The operational model will permit the necessary tradeoff studies to determine the effects of alternate design options including:

- high-speed color imaging sensor
- microscope video compression and windowing schemes
- high-bandwidth network approach (ISDN, ATM)
- interactive control

Figure 6 is illustrative of one such a tradeoff (in this case the relationship between the digitized field of view and the camera-imposed spatial resolution). During the design phase, all necessary hardware functions will be identified and alternate implementation approaches evaluated. Interface specifications for the candidate DPIM subsystems will be analyzed to assure compatibility and inter-operability. A critical activity will be identification and analysis of the factors that will affect interactive latency of the operational system (e.g., stage control, image acquisition, networking). Based on these evaluations, specific hardware will be identified for procurement under the implementation phase of the program. Table 3 provides an overview assessment of the current state-of-the art in CCD cameras. Table 4 compiles the key parameters of some of these commercially available cameras.

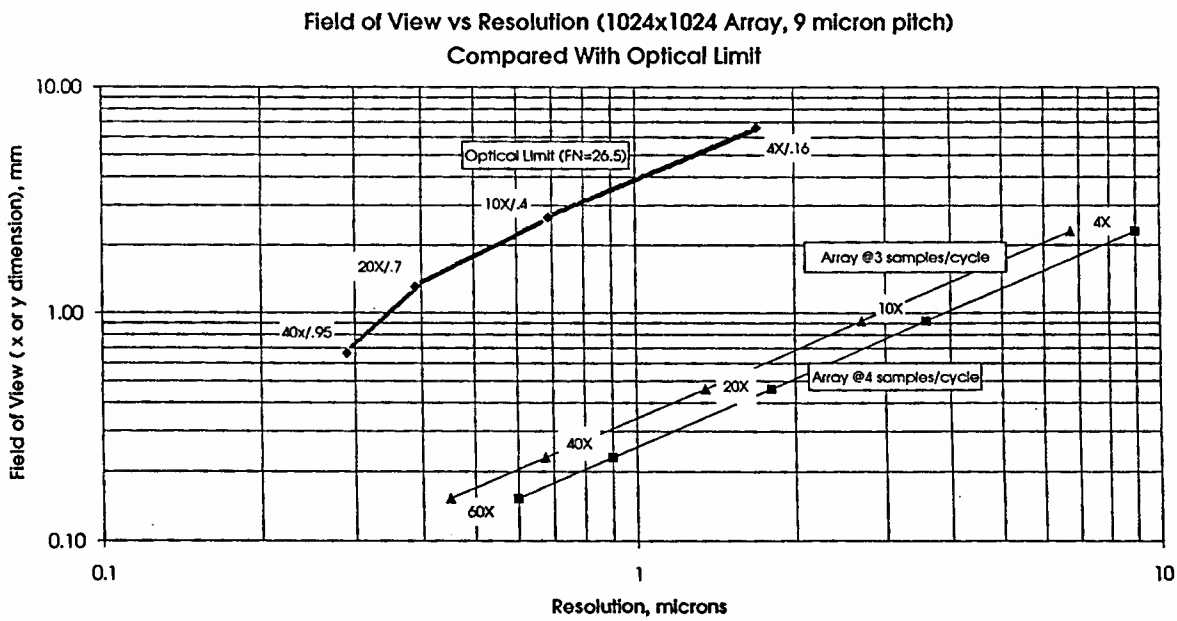


FIGURE 6. Digital Microscopy Field of View as a Function of Resolution

TABLE 3. Assessment of the Current State-of-the-Art for Commercial CCD Cameras

Assessment of Cameras for Interactive Microscopy

Camera Type	Technology	Representative Product	Advantages	Disadvantages
Color Still Camera	Single CCD array with integrated color striping filters	• Kodak DCS420 • Sony "CatsEye"	• Large array sizes (1524x1012) deliver greatest field of view for a given resolution • High sensitivity (up to 12 bits)	• Very long frame acquisition times (10-20 sec) • High cost
Color Video Camera	Three-CCD array with integrated color separation prisms	• Sony 960MD • Toshiba F55BU • Hitachi HV-C20M	• Real-time frame rates (30 fps) • Low cost • Mature color technology	• Limited array sizes limit field of view • Limited flexibility due to need to conform to existing NTSC standards
Monochrome Instrumentation Camera	Single CCD array, digital output	• Dalsa CA-D7 • Kodak Megaplus	• Modest frame rates (<30 fps) • Large array sizes deliver good field of view • High sensitivity (up to 12 bits) • Allows pixel binning (tradeoff resolution for light sensitivity)	• Requires external color separation filters • Requires three frame captures per color image • Moderate to high cost

TABLE 4. Specifications for Commercially Available High Resolution Digital Cameras

Hi-Res Camera	JVC	Dalsa	MegaPlus	ISIS	Axiom	Kodak	EG&G	Sony
Model	TK-F7300	CA-D7-1024	1.6I	VS-1	AX-2V	DCS 420	MD4013	960MD
Resolution, pixels	736x576 to 4416x3456	1024x1024	1534x1024	1536x1024	1536x1024	1524x1012	1024x1024	768x494x3
Pixel Size, microns		12x12	9x9	9x9	9x9	9x9	13.5x13.5	Non-Square
Color/Monochrome	C	M	M	Color Wheel	M	C	M	C
Bits/Pixel	24	8/12	10	12x3	12	36	8	Analog
Sec/Frame		.05, .125	1.5 to 5.5	1	4	40	> 0.1	1/60
Noise Level (e-)					13-20			
Integral Cooling	N	N	N	Y	Y	N	N	N
Interface	RGB Analog	RS422	RS422	RS422	Cust. Digital	SCSI	SCSI	NTSC/RGB
Cost	$9,495	$13,500	$11,000	$19,000	$12,000	$10,995		$6,480

2.3.2 Task 1.1.2: DPIM System Implementation

The implementation task will address 1) the procurement of the hardware subsystems, and 2) Lab integration and test of the DPIM.

Hardware Procurement

Based on the hardware specifications developed under Task 1, all hardware modules and subsystems will be procured. Table 5 is a preliminary, representative list of commercial components to be incorporated into the DPIM, with vendors and pricing shown. Vendor-provided driver software will be included as part of the hardware procurement.

TABLE 5. Preliminary Hardware Breakout for the DPIM

Subsystem	Typical Vendor (Model #)	Unit Cost	Quantity	Extended Cost
Workstation	HP9000 J-Class (J200)	VFE	2	VFE
Hi-Res Monitor,24bit color				
4GB Hard Drive				
Rewritable 1GB CD-ROM	CCG CY-2000	$4,000	1	$4,000
Frame Grabber (EISA)	Matrox, Imagraph	$6,000	1	$6,000
Color Calibrator	TBD	$5,000	1	$5,000
Tele-Conferencing	HP A4049A	$2,000	2	$4,000
Hi-Res Camera (mono.)	Dalsa CA-D7 1024T	$13,500	1	$13,500
Color Wheel	Ludl	$5,400	1	$5,400
Motorized Microscope	Olympus AX-80	$84,723	1	$84,723
Network Switch/Routers	Fore, Cisco	$21,000	1	$21,000
Pax-It	Pax-It	$17,000	1	$17,000
Kurzweil Voice Path	Kurzweil	$17,000	1	$17,000
Network I/F Cards&SW	Fore, Others	$5,500	2	$11,000
Misc. Cables, etc.	TBD	$3,000	1	$3,000
	TOTAL:	$184,123		$191,623

Lab Integration/Test

As the vendor-provided hardware and software is received, it will be incrementally integrated to verify stand-alone operation. A standard workstation platform (the HP J210) will be the central hub around which all other system components will be integrated and tested. Hardware/software latency times will be measured and deficiencies resolved as needed, particularly as the motorized microscope subsystem is brought on-line. Following stand alone test, the custom GUI software will be integrated and tested to ensure proper control of the application modules and lower-level drivers. A lab emulation of the fully networked system will be performed to verify remote operation and resolve any problems.

2.3.3 Task 1.1.3: DPIM System Integration/Test and Demonstration

Following successful lab integration at ERIM, the DPIM will be transported to the University of Michigan Department of Anatomy and Cell Biology and integrated on-site. Any site-specific debugging that may be necessary will be covered under this subtask. Remote operation between ERIM and UMICH will then be verified (as described under Task 3) and system performance characterized (e.g., latency measurements, etc.) to confirm predicted behavior. As described under Task 3, initial network demonstrations will link systems between UMICH and ERIM initially using Ameritech ISDN services. This will be followed by a phase-in of ATM, with ATM access and service provided by UMICH.

2.3.4 Task 1.1.4: AFIP System Replication

With this task, ERIM will procure, integrate, test, and deliver a duplicate DPIM system to AFIP. This task will include system setup and on-site test as well as integration of the DPIM network subsystems to an existing and compatible AFIP wide area network port.

2.3.5 Task 1.1.5: On-Site User Training

Upon successful integration of the remote station at AFIP, ERIM will conduct an on-site hardware training program to familiarize users of the DPIM with its operation. A hardware systems User Manual will be developed and provided to the operators.

2.3.6 Hardware Development Schedule

Table 6 lists the major milestones and schedule dates for the DPIM hardware development task.

TABLE 6. DPIM Hardware Development Milestones

Milestone	Description	Months After Start
1	Hardware Specification Completed	2.5
2	Begin Software Integration	3.5
3	DPIM Integrated/Tested at ERIM	8
4	DPIM Operational at UMICH	9
5	Second System Delivered to AFIP	11

2.4 Task 1.2: DPIM Software Development

Task 1.2 has been divided into 5 subtasks which are described below.

2.4.1 Task 1.2.1: COTS and GOTS Evaluation and Acquisition

The first task will involve the evaluation of COTS and GOTS software packages for use on this project. Packages of interest are GUI builders, client/server development tools, image processing and visualization tools, object-oriented databases, networked collaboration tools, PACS and DICOM tools, and pathology-specific software.

Software licenses and support will be purchased for the following systems:

- development system at ERIM

- delivery system for UMICH
- delivery system for AFIP

Table 7 contains a preliminary list of software packages to be evaluated for Task 1.2.

TABLE 7. Preliminary List of Software Packages to be Evaluated for Task 1.2

Package	Category
Visilog	Image Processing
AVS 5	Image Processing Visualization
AVS Express	Image Processing Visualization Application Development
Khoros	Image Processing Visualization Application Development
Versant	Object-Oriented Database
MergeCOM-3	DICOM Took Kit

2.4.2 Task 1.2.2: PAX-IT and Kurzweil System Evaluation

The PAX-IT systems will be installed at UMICH and ERIM and connected via ISDN. The system capabilities and user interface will be evaluated with respect to the requirements for this project. Our intention is to follow conventions in the medical field for the DPIM interface whenever possible so that users familiar with other equipment will be comfortable learning and using the DPIM.

It is recognized that voice recognition capability is a key component of a future deployable DPIM. It is important to develop an understanding of the current state-of-the-art in voice recognition in order to determine the best path to integration of this capability into the DPIM. To this end, the Kurzweil AI pathology voice recognition system will be installed on the PAX-IT computer and evaluated. Recognition performance in the pathology domain and the facilities for integration with our software will be studied.

2.4.3 Task 1.2.3: DPIM System Software

The DPIM system software will integrate a variety of capabilities into an environment with a uniform and user-friendly GUI. The most critical component of this software is for the control of microscope, camera, and frame grabber hardware. Components that increase the utility of the DPIM include from the user's standpoint include image processing capability, database storage and retrieval, video conferencing, and whiteboard conferencing. Capabilities that increase the utility of the DPIM as prototype for a deployable system include DICOM compatibility, ISDN networking, and ATM networking.

The DPIM system software will include special-purpose software which bridges the gap between simply controlling the hardware and producing useful output data. Color calibration is one example of this type of software that has been identified.

General-purpose image processing capability will be required by the serious DPIM user because the DPIM is intended to be applied to a wide variety of pathology and other medical imaging problems. No set of canned routines will be sufficient. This capability will make it possible to interactively perform standard image processing operations on images being captured by the microscope and on previously saved images and then to display or save the results.

An object-oriented database implemented with the Versant database system will be integrated into the DPIM software. It will handle storage and retrieval of images and associated data. The information associated with an image will include collection parameters which will be automatically captured and stored by the system as well as information provided by users. The user will be able to add additional information such as comments, annotations, or diagnoses to images. Images will be retrievable using the associated information that is saved with the images.

Software support for DICOM standards will be developed as necessary. It is intended that the DPIM be as DICOM-compliant as possible within the constraints of the program, the DICOM standard, and available DICOM tools. Software support for TCIMS will be developed as necessary.

The HP video conferencing system will be integrated into the DPIM software. Both the video conferencing and the whiteboard conferencing capabilities are important to successful remote operation of the DPIM.

The DPIM software will make use of networking capabilities developed and tested under the networking task. The DPIM software will be designed to support ethernet, FDDI, ATM, and ISDN in a manner that is transparent to the user. Initially, only local operation will be supported. Remote operation capabilities will be developed and tested in parallel with the network development tasks. The final system will support coordination of control between local and remote users.

2.4.4 Task 1.2.4: Pathology Application Development

In consultation with UMICH, ERIM will identify a pathology-specific application, such as cell counting, for demonstration purposes. Appropriate data will be obtained from UMICH, algorithms will be developed, and a demonstration videotape will be produced and delivered to ARPA. Consultants from the UMICH Department of Pathology and from AFIP will provide the necessary pathology expertise to the ERIM algorithm developers. Software and datasets developed on this task will be delivered to UMICH.

2.4.5 Task 1.2.5: DPIM System Documentation

Documentation will be provided in HTML format for easy access by the workstation user and over the WWW. An HTML authoring tool will be purchased to assist in the production of high-quality documentation.

2.4.6 DPIM Software Development Milestones

Milestones for the development of the DPIM software are presented in Table 8.

TABLE 8. DPIM Software Development Milestones

Milestone	Description	Months After Start
1	Evaluation of Software Resources Completed	3
2	Baseline Software Developed	7
3	DPIM Operational at UMICH	9
4	Pathology Application Developed	12
5	Delivery of Videotape Demonstration	12
6	Final System Documentation Delivered	18

2.5 DPIM Development Schedule

A detailed schedule of the DPIM development activities is shown in Figure 7.

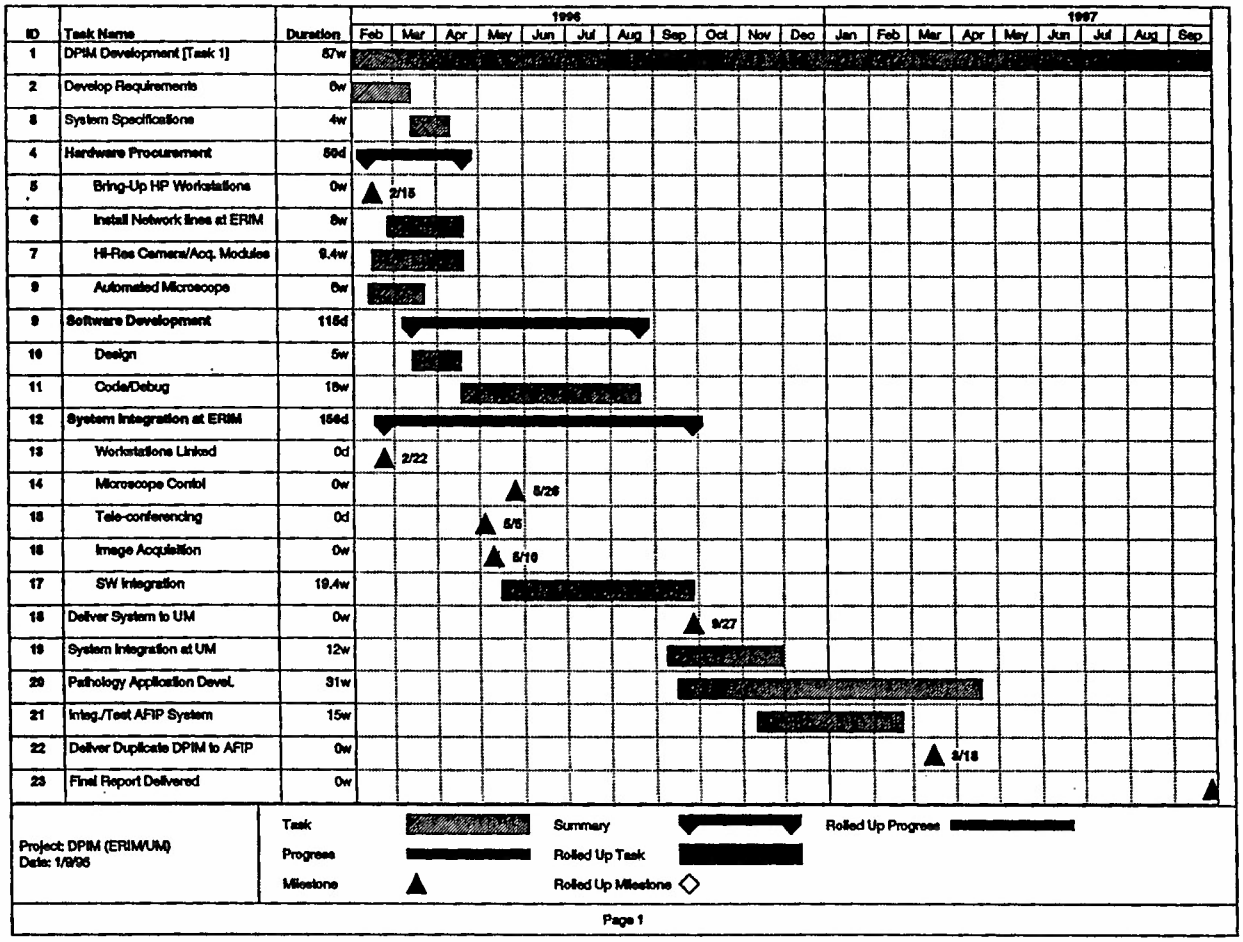


FIGURE 7. DPIM Development Schedule

3.0 Task 2: 3-D Processing and Visualization

Three dimensional data sets provide a wealth of information to pathologists for diagnosis and prognosis. Technical feasibility is not the same as ease or practicality in three dimensional study of cells and tissues. Three-dimensional data sets put a premium on data acquisition, data storage, computer processing and display, and demand very high bandwidth data transmission capability for distributed utilization. This task is directed toward bringing 3-D imaging into the reach of practical pathology applications by assessing, developing, and demonstrating the near-term state-of-the-art and providing focussed recommendations for longer-term development.

Most pathologists extrapolate visual information from two dimensions to three, often for many coplanar images per specimen. Recently, investigators have begun to work with coaxial stacks of images representing specimens at the cellular or tissue level. Such work is driven partly by new biological applications (e.g. interphase cytogenetics) that probe cell biology. Work is also driven simply by developments in microscopy (e.g. confocal imaging) and image processing (e.g. volume rendering) that bring three dimensional data acquisition and display within reach for some laboratories. One application of that technology is in study of tissue structures such as renal glomeruli.

Most investigations involving 3-D visualization and analysis are performed in a research setting. The specimen preparations and instruments used to acquire 3-D data sets are complex compared to those used for traditional bright field microscopy. The skills needed for image processing, rendering and analysis are beyond the training of nearly all pathologists, even in academic settings. Few, if any, individuals possess all the expertise needed to exploit current imaging technology for the practice of pathology. However, development of the field can move forward with work from individuals with overlapping subsets of the required expertise. In the foreseeable future, effective application of 3-D imaging methods to pathology will require interactive input from pathologists, expert microscopists, and computer scientists, such as are represented on the UMICH-ERIM-AFIP team.

Task 2 has been divided into 4 subtasks which are described below.

3.1 Task 2.1: COTS and GOTS Evaluation and Acquisition

The first task will involve the evaluation of COTS and GOTS software packages for use on this project. Packages of interest are general-purpose image processing and visualization tools as well as pathology specific and confocal microscopy-specific tools.

After the evaluation process, software products suitable for use on this project will be identified and licenses and support will be purchased.

Table 9 contains a preliminary list of software packages to be evaluated in Task 2.

TABLE 9. Preliminary List of Software Packages to be Evaluated in Task 2

Package	Category
Visilog	Image Processing
AVS 5	Image Processing Visualization
AVS Express	Image Processing Visualization Application Development
Khoros	Image Processing Visualization Application Development

3.2 Task 2.2: Visualization Generation

ERIM will generate visualizations of 3 datasets to be provided by UMICH. Currently identified datasets are:

- A triple-label 3-D LSCM dataset of the Organ of Corti (inner ear). This object has been selected because it is the most complex of all biological tissues.
- A triple-label 3-D LSCM dataset of embedded electrodes interacting with labelled neurons and glial cells in the brain.
- A serially-sectioned, histologically stained temporal bone dataset.

It is anticipated that a significant number of 2-D and 3-D image processing steps will be required in order to develop useful visualizations. Thus, as necessary for the production of the visualizations, a variety of algorithms will be developed. ERIM will draw upon its broad range of experience in image processing algorithm development and visualization in medical and non-medical domains during the development process. We have identified some algorithms that are likely to be needed but will modify this list as appropriate after receiving the image data:

- color calibration
- color data compression
- 2-D and 3-D mosaicking
- 2-D mosaic from adjacent images
- 3-D mosaic from confocal stack or sections
- combined 2-D and 3-D mosaic
- color image restoration
- deconvolution
- segmentation
- microscope-specific visualization

The datasets and the software developed during the production of the visualizations will be delivered to UMICH. The datasets and software will be available to both UMICH and AFIP for research and demonstration purposes.

3.3 Task 2.3: Videotapes of Visualizations

Videotapes of the visualizations of the three datasets will be produced and delivered to UMICH. The videotapes will include a "fly-through" of the dataset and will also show a user interacting with the visualization tools to view particular aspects of the dataset.

3.4 Task 2.4: Software Documentation

The delivered software will be documented using HTML format for viewing with a WWW browser.

3.5 3-D Processing and Visualization Milestones

Milestones for this task are presented in Table 10.

TABLE 10. 3-D Processing and Visualization Milestones

Milestone	Description	Months After Start
1	Evaluation of Software Resources Completed	4
2	3-D Microscopy Software Developed	7, 12, 17
3	Visualization Tools Developed	7, 12, 17
4	Visualization Generated	8, 13, 18
5	Videotape Demo Delivered	8, 13, 18

4.0 Task 3: Networking Demonstrations

4.1 Networking Demonstration Support

Under this task, ERIM will support UMICH (the demonstration coordinator) in the incremental demonstration and evaluation of networked operation of the DPIM. These progressive demonstrations will ultimately illustrate high-bandwidth WAN connectivity of the DPIM between UMICH and AFIP. The progression of demonstrations will be:

- ERIM-UMICH via ISDN; PAX-IT at ERIM, PAX-IT at UMICH
- ERIM-UMICH via ISDN; DPIM at ERIM, workstation at UMICH
- UMICH-UMICH via ATM; workstation and DPIM at UMICH
- ERIM-UMICH via ATM; workstation at ERIM, DPIM at UMICH
- AFIP-UMICH via ATM; workstation (or DPIM) at AFIP, DPIM at UMICH

ERIM's role during these demonstrations will be to install previously tested (by UMICH) networking hardware and software into the DPIM and to provide technical support to UMICH during integration, debug and performance evaluation within the various network configurations. This task includes integration support at AFIP during demonstration phase 5.

Also supported under ERIM's Task 3 activities will be: 1) the installation and test of an in-house ATM network backbone between the ERIM laboratory and the ERIM external demarcation point; and 2) installation and leasing of ISDN PRI (1.5 Mbps) service between the ERIM laboratory and the local Ameritech switching office.

All other network infrastructure and service will be provided by UMICH. Therefore, prerequisites to ERIM's Task 3 activities include the following functions to be performed by UMICH:

- Installation and lease of ATM backbone between UMICH laboratory and the ERIM external demarcation point
- Installation and lease of ISDN PRI service (1.5Mbps) between UMICH laboratory and the local Ameritech switching office.
- provision of ATM service between UMICH and AFIP, including arrangements for local ATM installation at AFIP.

4.2 Networking Demonstration Milestones

Milestones for the planned demonstrations are shown in Table 11.

TABLE 11. Networking Demonstration Milestones

Milestone	Description	Months After Start
1	ERIM-UMICH ISDN using PAX-IT Systems	3
2a	ERIM-UMICH ISDN using Workstation and DPIM —DPIM at ERIM, Workstation at UMICH	7
2b	ERIM-UMICH ISDN using Workstation and DPIM —DPIM at UMICH, Workstation at ERIM	9
3	UMICH ATM LAN using Workstation and DPIM	12
4	ERIM-UMICH ATM WAN using Workstation and DPIM	15
5	AFIP-UMICH ATM WAN using Workstation and DPIM	18

5.0 Statement of Work

5.1 Task 1: DPIM System Development and Delivery

5.1.1 Task 1.1: DPIM Hardware Development

Task 1.1.1: DPIM System Specification and Design

- Perform trade off analysis between performance goals, available technology, and cost.
- Design the DPIM system to optimize performance goals, technology, and cost goals.
- Specify hardware components of the DPIM system.

Task 1.1.2: DPIM System Implementation

- Purchase all required hardware for the DPIM system.
- Test components individually.
- Integrate components into the DPIM system.
- Integrate software developed on Task 1.2 into the DPIM system.
- Test the DPIM system and evaluate its performance.

Task 1.1.3: DPIM System Integration/Test and Demonstration

- Deliver the DPIM system to UMICH and install it.
- Test the DPIM system and evaluate its performance at UMICH.

Task 1.1.4: AFIP System Replication

- Purchase all required hardware for the AFIP DPIM system.
- Integrate hardware for duplicate DPIM system.
- Test the DPIM system at ERIM.
- Deliver the DPIM system to AFIP and install it.
- Test the DPIM system at AFIP.
- Integrate and test DPIM with AFIP network connection.

Task 1.1.5: On-Site Training at AFIP

- Provide one week of hardware and software training at AFIP.
- Deliver hardware users manual.

5.1.2 Task 1.2: DPIM Software Development and Integration

Task 1.2.1: COTS and GOTS Evaluation and Acquisition

- Perform evaluation of COTS and GOTS software packages for use on this task.
- Based on the results of the evaluation, purchase licenses and support for software packages as needed for this task for the following systems:
  - development system at ERIM
  - delivery system for UMICH
  - delivery system for AFIP

Task 1.2.2: PAX-IT and Kurzweil System Evaluation

- Evaluate the capabilities of the PAX-IT system installed and connected under tasks 1.1 and 3.
- Install Kurzweil AI pathology voice recognition system on the PAX-IT computer and evaluate its capabilities.

Task 1.2.3: DPIM System Software

- Develop software and graphical user interface to control the DPIM hardware (microscopes, camera, frame grabber, networking hardware).
- Integrate image processing capability into the DPIM software.
- Integrate the HP video conferencing system into the DPIM software.
- Integrate an object-oriented database into the DPIM software.
- Develop other software required for the function of the DPIM as necessary.

Task 1.2.4: Pathology Application Development

- Identify and implement a pathology-specific application for demonstration purposes, in conjunction with UMICH and AFIP consultants.
- Obtain appropriate data, develop algorithms, produce demonstration videotape, and deliver videotape to UMICH.

Task 1.2.5: DPIM System Documentation

- Develop documentation for the DPIM software. It will be provided in HTML format for easy access by the workstation user and over the WWW.

5.2 Task 2: 3-D Processing and Visualization

Task 2.1: COTS and GOTS Evaluation and Acquisition

- Perform evaluation of COTS and GOTS software packages for use on this task.
- Based on the results of the evaluation, purchase licenses and support for software packages as needed for this task for the development system at ERIM.

Task 2.2: Visualization Generation

- Generate visualizations of 3 datasets to be provided by UMICH.
- Develop software as necessary for the production of the visualizations.
- Deliver to UMICH data sets and software developed during the production of the visualizations. The data sets and software will be available to both UMICH and AFIP for research and demonstration purposes.

Task 2.3: Videotapes of Visualizations

- Produce videotapes of the visualizations of the three datasets and deliver them to UMICH.

Task 2.4: Software Documentation

- Develop documentation for the DPIM software. It will be provided in HTML format for easy access by the software user and over the WWW.

5.3 Task 3: Network Demonstrations

Under Task 3, ERIM will provide support for ERIM's role in the following networking demonstrations:

- ERIM-UMICH ISDN using PAX-IT Systems
- ERIM-UMICH ISDN using Workstation and DPIM
  - DPIM at ERIM, Workstation at UMICH
  - DPIM at UMICH, Workstation at ERIM
- UMICH ATM LAN using Workstation and DPIM
- ERIM-UMICH ATM WAN using Workstation and DPIM
- AFIP-UMICH ATM WAN using Workstation and DPIM

To support these demonstrations, ERIM will:

- Install and lease ISDN PRI (1.5 Mbps) service between the ERIM laboratory and the local Ameritech switching office.
- Install and test an in-house ATM network backbone between the ERIM laboratory and the ERIM external demarcation point.
- Install networking hardware and software previously tested (by UMICH) into the DPIM.
- Provide technical support to UMICH during integration, debug and performance evaluations.
- Provide integration support at AFIP during the UMICH-AFIP ATM WAN demonstration.

ERIM's proposal assumes that UMICH will provide all other network infrastructure and service, including:

- Install and lease ATM backbone between UMICH laboratory and the ERIM external demarcation point.
- Install and lease ISDN PRI service (1.5Mbps) between UMICH laboratory and the local Ameritech switching office.
- Provide ATM service between UMICH and AFIP, including local ATM infrastructure at AFIP.

6.0 Schedule

Figure 8 contains a schedule of milestones for the project assuming a start date of January 31, 1996.

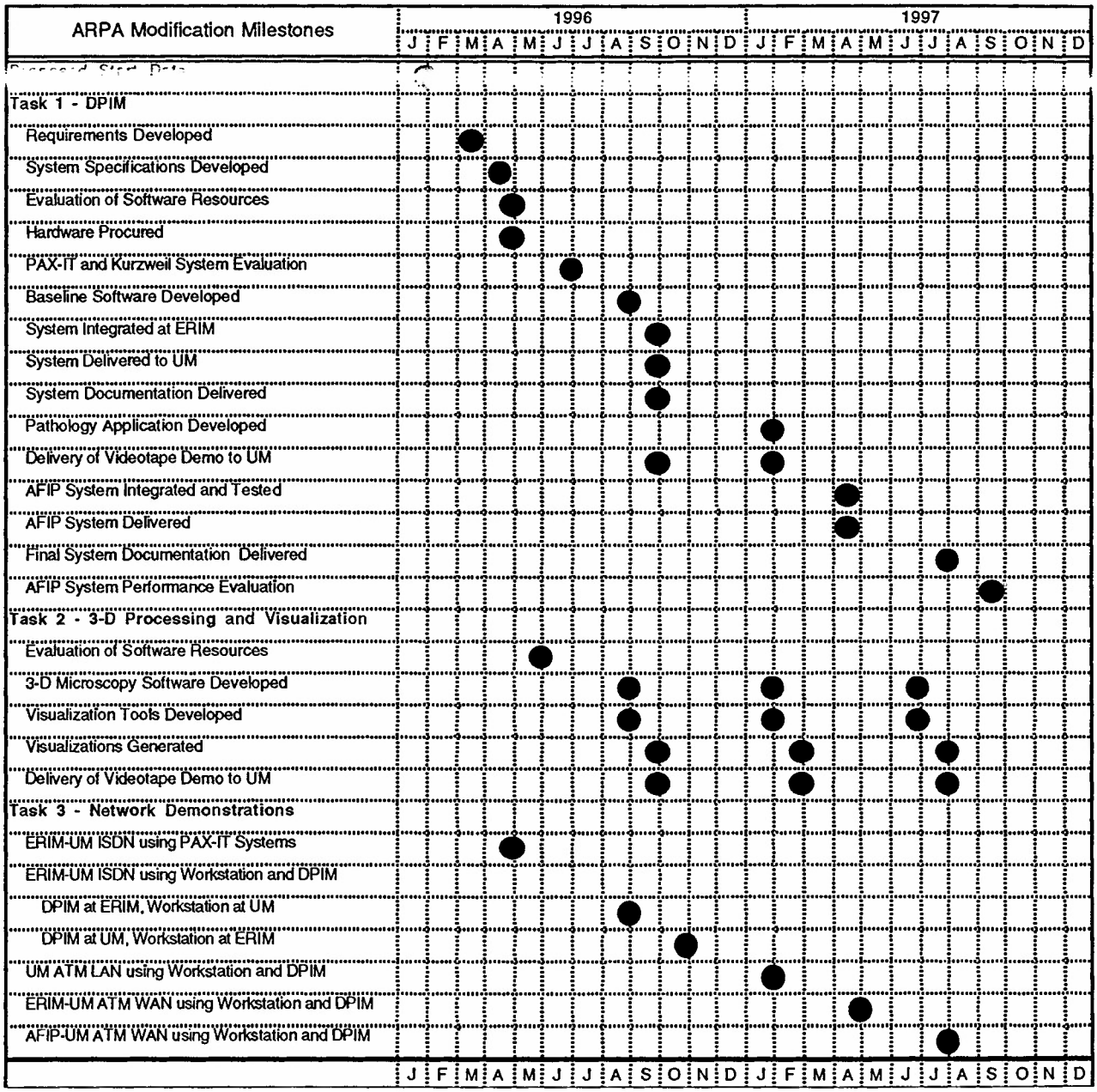


FIGURE 8. Schedule of Milestones

A twenty-month program is planned, with demonstrations at approximately three month intervals. Acquisition and integration of components of the first DPIM is scheduled to be completed during FY 96, presuming that the program can be initiated early in the second quarter. Acquisition and integration of components of the second DPIM, for delivery to the AFIP, is planned for FY 97. The 3-D datasets will be developed over a period of approximately 18 months, with videotaped demonstrations scheduled at approximately 6 month intervals. It is anticipated that tool development will continue throughout the program and that the visualizations will be regenerated to demonstrate the improved capability. The schedule of network demonstrations follows closely the schedule for the DPIM development. A first demonstration using the COTS PAX-IT system is scheduled at 3 months, with the first DPIM demonstration at the end of FY 96, prior to delivery to UMICH. Subsequent demonstrations are planned at 3 month intervals. The schedule shown in Figure 8 will need to be revised if ERIM's start date is delayed, or if there are delays in the delivery of components or data to ERIM from UMICH or vendors.

7.0 Cost Summary

Table 12 summarizes the anticipated costs of Tasks 1, 2, and 3 as described in Sections 2 through 4, above. Details and supporting information are provided in the accompanying Cost Proposal (Volume II of this proposal).

TABLE 12. Summary of Costs by Task and Fiscal Year

Task	FY 96 Costs ($K)	FY 97 Costs ($K)	Total ($K)
Task 1: DPIM System Development and Delivery	1016.9	599.0	1615.9
Task 1.1 DPIM Hardware Development	356.0	151.3	507.3
1.1.1 System specification and design	113.5		113.5
1.1.2 System implementation	215.3		215.3
1.1.3 System integration and testing	24.7	56.6	81.3
1.1.4 AFIP system replication		66.4	66.4
1.1.5 On-site training (AFIP)		20.8	20.8
1.1.6 Travel	2.5	7.5	10.0
Task 1.2 DPIM Software Development	378.4	122.2	500.6
1.2.1 COTS and GOTS software evaluation	25.2		25.2
1.2.2 PAX-IT and Kurzweil evaluation	27.7		27.7
1.2.3 DPIM software design, development and integration	226.9		226.9
1.2.4 Pathology application software development		98.0	98.0
1.2.5 DPIM software documentation	23.9	14.3	38.2
1.2.6 Development software purchases	67.5		67.5
1.2.7 Travel	7.2	9.9	17.1
Task 1.3 DPIM Pathology Consulting	25.7	25.6	51.3
1.3.1 Consulting time	20.3	20.3	40.6
1.3.2 Consultant travel	5.4	5.3	10.7
Task 1.4 UMICH DPIM System Components	256.8		256.8
1.4.1 UMICH DPIM hardware	243.5		243.5
1.4.2 UMICH DPIM software	13.3		13.3
Task 1.5 AFIP DPIM System Components		299.9	299.9
1.5.1 AFIP DPIM hardware		286.6	286.6
1.5.2 AFIP DPIM software		13.3	13.3

TABLE 12. Summary of Costs by Task and Fiscal Year (Continued)

Task	FY 96 Costs ($K)	FY 97 Costs ($K)	Total ($K)
Task 2. 3-D Processing and Visualization	160.7	197.8	358.5
Task 2.1 COTS and GOTS software evaluation	21.4		21.4
Task 2.2 Visualization generation	90.1	163.7	253.8
Task 2.3 Videotaped demonstrations	10.5	17.8	28.3
Task 2.4 Software documentation	23.9	9.1	33.0
Task 2.5 Development software purchases	7.6		7.6
Task 2.6 Travel	7.2	7.2	14.4
Task 3: Networking Demonstrations	54.8	76.9	131.7
Task 3.1 Demonstration support	31.2	67.3	98.5
Task 3.2 Network infrastructure and telco charges	23.6	7.1	30.7
Task 3.3 Travel		2.5	2.5
Total	1232.4	873.7	2106.1

8.0 Disposition of Equipment and Software

Hardware components of the DPIM purchased by ERIM and integrated under Task 1 (specified in Table 5, Section 2.3.2) will be titled to the University of Michigan and delivered to the Principal Investigator and AFIP. All other equipment and software purchased by ERIM under the proposed subcontract will be titled to ERIM and placed at ERIM. This proposal assumes that two Hewlett-Packard J9000 workstations will be supplied to the project without charge by Hewlett-Packard Federal. One of these workstations will be integrated into the DPIM in Task 1 and delivered by ERIM to the University of Michigan with the DPIM. The second workstation will be used for software development and demonstration; this workstation will be placed at ERIM throughout the program and will remain at ERIM indefinitely unless returned to the vendor.

9.0 Biographies

9.1 Laurel Harmon, Ph.D.
Program Manager

Dr. Harmon is a Research Manager at ERIM, heading the Symbolic Processing Department in the Information and Materials Applications Laboratory. Dr. Harmon received her Ph.D. in Physical Chemistry from the University of Michigan in 1985. Since that time, she has been active in program and technical management on a variety of projects at ERIM. Currently, Dr. Harmon manages ERIM's Electron Micrograph Analysis program, which involves computer-assisted analysis of electron micrographs on a production basis for Hoffmann-La Roche, under subcontract to the University of Michigan. She recently managed programs to develop a large-scale data management system for target recognition and to apply artificial intelligence techniques to diagnostic radar imagery. Dr. Harmon previously managed ERIM's Automatic Reference Data Extraction program, which involved extraction of geometric and feature information from image, MC&G, and intelligence sources to construct a three-dimensional database description of a target area and surrounding terrain. She was also program manager for the Machine-Print Character Recognition program, which involved large-scale on-site data collections of postal image data, and the development and testing of high performance character recognition algorithms. Other responsibilities have included management of technical efforts on programs to evaluate Automatic Target Cueing Technology and development of fractal scene segmentation algorithms for synthetic aperture radar (SAR) imagery. Additional activities have involved computer simulation of a sensor fusion system and incorporating multiple sensor models and decision logics into a flexible software architecture for system modelling. Prior experience at ERIM entailed task and program leadership on ARPA-sponsored programs related to the Autonomous Land Vehicle program.

9.2 Paul Mohan
Task Leader, DPIM System Development and Delivery

Mr. Mohan holds the position of Research Manager and has been an ERIM employee since 1979. He heads the Systems Engineering and Hardware Integration department within ERIM's System Engineering and Integration Center. Mr. Mohan received his MS degree in Electrical Engineering from the University of Illinois and has 18 years of experience in the development and implementation of specialized systems for real-time signal and image processing. During this time, his work has covered a broad spectrum of application areas and has applied both custom and commercial processing elements. He recently completed a design study for an interactive biomedical interpretation station that would give pathologists full remote capability and enable high-volume biomedical screening. Mr. Mohan has considerable experience in high-bandwidth data communications and was responsible for definition and field implementation of the tele-communication links for image transfer between remote sites during a recent US government field exercise. He headed the electronics development efforts for the ATCURE program, overseeing the specification and design of an advanced, miniaturized target cueing and recognition engine. He is co-author of a number of related contract-funded study reports including: MSRC Surveillance System Design Trade Study, and Remote Minefield

Detection System Real-Time Architecture Study. Mr. Mohan holds two patents in related fields of electronics with a third pending award.

9.3 Paul Kortesoja
Lead, DPIM Hardware Development
Task Leader, Networking Demonstration Support

Mr. Kortesoja is a Research Engineer in the Systems Engineering and Hardware Integration department within ERIM's System Engineering and Integration Center. Mr. Kortesoja received a BS degree in Computer Engineering at the University of Michigan. He joined ERIM in 1984 after work at the Applied Physics Laboratory (Johns Hopkins University) on the U.S. Navy AEGIS program. Mr. Kortesoja's current work is concentrated in the area of hardware and systems development and delivery. His responsibilities include management of and participation in new image processing hardware designs, definition and assessment of image processing system architectures, system integration, testing delivery, and maintenance. He was production manager for the UM-ERIM project for Hoffmann-La Roche to image nerve biopsies using digital electron microscopy. Mr. Kortesoja also manages ERIM's on-going biomedical imaging system development for Eli Lilly and Mr. Kortesoja served as the System Development Task Leader for the Advanced Target Cueing and Recognition Engine (ATCURE) program. He was responsible for oversight and coordination of all system development activities. Other related areas of responsibility have included digital hardware design, software design and maintenance for ERIM's proprietary image processing language, and the design and development of hardware test and verification software.

9.4 Alan Vayda, Ph.D.
Lead, DPIM Software Development
Task Leader, 3-D Processing and Visualization

Dr. Vayda is a Research Engineer in the Symbolic Processing Department of ERIM's Information and Materials Applications Laboratory. He received his Ph.D. in Electrical Engineering from Purdue in 1991. Dr. Vayda's interests include 2-D and 3-D computer vision, medical image processing, robotics, evidential reasoning, logic programming, geometric reasoning, contextual reasoning, and advanced database technology. As part of Dr. Vayda's thesis research at the Purdue Robot Vision Lab he developed a 3-D robot vision system for the recognition and manipulation of postal objects in heaps. Generic 3-D object models and geometric reasoning about physical constraints between objects were used for recognizing the shape and dimensions of postal parcels. Since coming to ERIM, he has had extensive experience in management and technical aspects of programs to develop and deliver large-scale software systems. Dr. Vayda is currently managing ERIM's Performance Evaluation of ATR Systems (PEATRS) program, which is developing a large-scale heterogeneous data management system for all of the data associated with radar data collections and ATR algorithm development and testing. Prior to assuming PEATRS program management, Dr. Vayda designed the ATR data management environment, which facilitates ATR algorithm evaluation by integrating heterogeneous information from many sources for easy access through a user-friendly graphical user interface (GUI). It is being implemented with an Oracle RDBMS and a one-terabyte-sized Hierarchical File System. The Khoros application development environment is being used for GUI development, visualization, and image processing func-

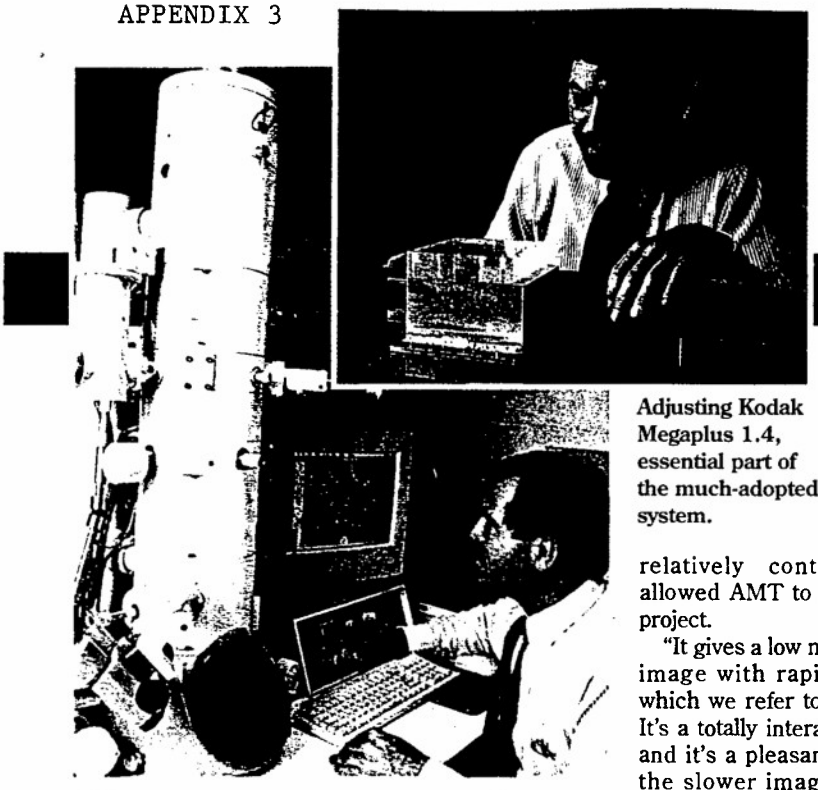
tionality. The system prototype used the POSTGRES object-relational database and the GRASS GIS. Dr. Vayda has also been involved in the database design and implementation on ERIM's Electron Micrograph Analysis project, using the Versant ODBMS and the Argos development environment. Prior experience at ERIM includes program management for ERIM's Contextual Analysis project for the USPS, involving reading and interpretation of addresses on mailpiece images as well as research on applying 3D range sensor technology to minimally-invasive Neurosurgery.

APPENDIX 3

Daylight for Electron Microscopists:

GROWING CCD SOLUTION

By Leigh Grimm



Adjusting Kodak Megaplus 1.4, essential part of the much-adopted system.

AMT's James Mancuso, working with TEM images and sharing them—with the lights on.

Electron microscope level images viewed in broad daylight, easily shared and printed? High-speed interactivity for those in the medical, biological and material research market using transmission electron microscopy—TEMs? Yes. Now. And at the desktop computer level.

Advanced Microscopy Techniques (AMT), out of Rowley MA, has delivered all this, providing the speed and sensitivity increasingly sought after in bio and material science apps through the integration of the light-sensitive Kodak Megaplus camera and their Advantage Series of TEM digital image capture systems. With about 100 electron microscopes now sold each year around the country, last year AMT sold 40 interfaces with CCD cameras for image analysis and processing.

The AMT system consists of the microscope, of course, which is first purchased by the AMT client from leading TEM manufacturers, a phosphor and optical coupler (lens), the Kodak CCD camera, and the framegrabber for PC or Mac, which are provided by AMT. The client can then add printers and anything else needed for their specific application.

This system is for "anyone who's being forced or wants to get into the world of storing digital images; anyone who's trying to eliminate chemical waste from the photographic process; and those who want to do digital analysis," AMT's James Mancuso told us. "We'd decided to incorporate the Kodak Megaplus camera into the system because it was un-cooled, sensitive and fast," as clients in these apps needed. Mancuso says the camera's simplicity and relatively controlled cost allowed AMT to get into this project.

"It gives a low noise, high res image with rapid response, which we refer to as live-time. It's a totally interactive system, and it's a pleasant solution to the slower imaging systems previously used," Mancuso told us, "cameras typically designed for astronomy."

To date, more than half of AMT installations include the Kodak Megaplus camera, model 1.4 (with 1.4 million pixels), which is, of course, specifically designed to be integrated into image processing/analysis systems. For some applications, AMT employs the model 1.6 which recognizes 1,024 distinct shades of gray. This feature has proven ideal for TEM, where fine detail is critical, by definition.

Benefits of this cameras integration for AMT's clients include: much faster turn around time in diagnosis; reduction of cost because less film and labor is needed; and growing use as an instructional tool because it can be used in a lighted room. (Other systems with less sensitive cameras have required a dark room for viewing captured TEM images.)

Microscopists can now view images on monitors in lighted rooms, share critical information with colleagues over a network and insert digital images in reports in minutes.

Acceptance and use

AMT's direct sales have reportedly quadrupled in just one year. The firm sells directly to microscope manufacturers such as Philips and Zeiss; other customers include national labs, hospitals, industrial research facilities and medical schools, such as the Universities of Georgia, Nebraska and Michigan.

As AMT's Mancuso put it, "We're always concerned with what our clients want to use the system for. We get involved." Frequently, after someone has purchased a microscope, the company will receive a call by one of the vendors, and the process of putting together a customized system can begin.

Adopter impact?

• The anatomy and cell biology department at the University of Michigan School of Medicine uses the AMT system to study human nerve structure and regeneration.

A research team currently analyzing the effect of an experimental compound to combat the degenerative effects of diabetic peripheral neuropathy, a painful and debilitating disease, has been pulling together 500 montages of nerve fascicles which, at this high resolution, comprise virtual images measuring 25 to 30 feet in diameter. The Kodak Megaplus digital camera, model 1.6, in tandem with the Philips CM 100 electron microscope, are the basis of the project.

To assemble the images after they have been captured, the team uses software developed by imaging specialists ERIM (the Environmental Research Institute of Michigan), in collaboration with AMT and Philips. Once the virtual image is assembled, it is then divided into manageable units called tiles, for computer storage and transmission.

• The AMT system has also found a niche in industrial personal product research. R. P. Gursky is a principle research microscopist at Unilever Research U.S. (Edgewater NJ). In his research activities, Gursky and his team require a huge amount of documentation that can be easily viewed, shared and incorporated into reports in a timely manner. This system allows him to have images in front of him right away and to call up 20 to 30 images in a group and discuss them, fast. Gursky's team also moves these images around a network, so a researcher in another building can see the same image at the same time and collaborate.

In the next several months, researchers will be able to incorporate digital images directly into their reports, allowing them to get project reports out in real time without cutting and pasting and weeks of darkroom art.

For more info about AMT's digital image capture system: contact James Mancuso, AMT president at (508) 774-5550, or Circle 304.

For more info on the Kodak Megaplus camera, contact Wendy Telford at (619) 535-2909, or Circle 305. ■

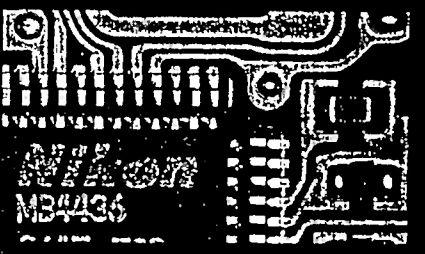
Nikon

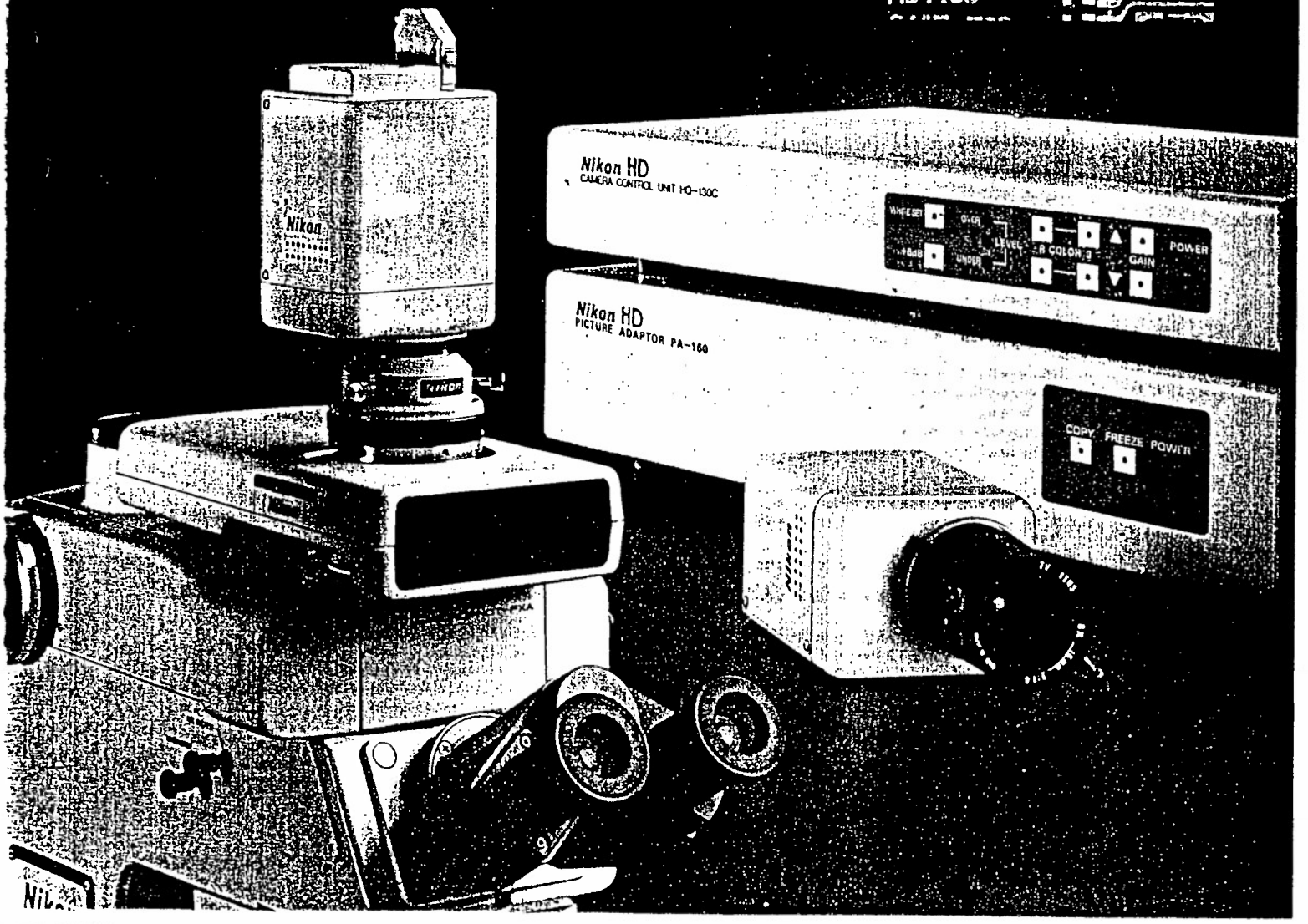
High-Definition Color Camera System

HQ-130C

English text for reference only
(Product not yet available outside Japan)

Incorporating a 1.3 million pixel CCD
Offering crisp, sharp, high-definition images

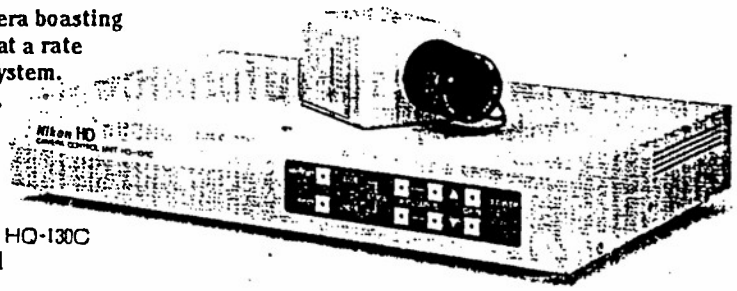




In a light and compact design, the HQ-130C f for new high-definition color image applicat

A71

The Nikon HQ-130C is a 2/3-inch, high-definition color CCD camera boasting a 1.3 million pixel resolution. The HQ-130C can capture images at a rate of one frame per 0.05 seconds thanks to the RGB rotating disk system. In combination with the HD Picture Adapter PA-160 series, crisp, high-definition images can be displayed on the monitor screen in real time. Coupled with its high-speed image capture characteristics, the HQ-130C camera offers excellent image tracking comparing well with movie cameras. Weighing as little as 500g, the compact, high-performance HQ-130C is up to the most demanding challenges in the medical and industrial fields.



HQ-130C

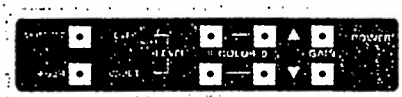
High-definition color CCD camera HQ-130C

1.3 million pixel CCD
With a 2/3-inch, 1.3 million pixel CCD, the HQ-130C allows you to capture stable images and obtain a high signal-to-noise ratio.

High-speed image capture
Employing the RGB rotating disk system, the HQ-130C makes high-speed* image capture as fast as 0.05 sec. per frame possible, with excellent tracking capability just like a movie camera.
*0.05 sec./frame (in detection mode), 0.1 sec./frame (in non-detection mode)

Light and compact design
With the camera head weighing a mere 500g, you can easily connect the camera head to the camera control unit via a single camera cable.

Comprehensive image quality compensation functions
All compensation control buttons and indicators including gain control (+6 dB), white balance setting, color compensation and LED light amount indicators are all located on the front panel of the camera control unit. Horizontal contour compensation control function is also provided.

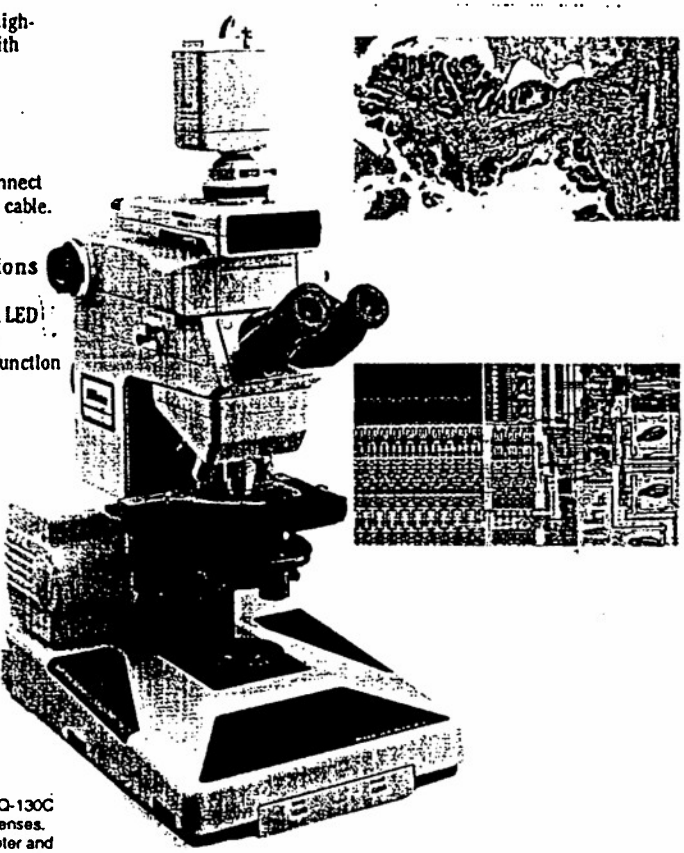


Using the C mount
The generally accepted C mount is employed for easy mounting of the HQ-130C on biological and industrial microscopes. Various types of C mount lenses*** can also be mounted.

The C-mount TV adapter or ENG-C TV adapter is necessary when mounting the HQ-130C on biological and industrial microscopes.
C mount lens**: Directly mountable
Nikkor lens***: Use F-C mount adapter

**High performance C mount lenses are recommended otherwise the HQ-130C cannot perform to its full potential. Please ask Nikon for recommended lenses.
*** Auto and manual exposure control is possible with dedicated AI adapter and Operation Unit OU-160.

New high-definition color image applications
Medical field: Image observation and operations recording using biological and medical operation-use microscopes.
Industrial field: Image observation, analysis, and measurement of semiconductors and electronic parts using industrial microscopes.



High-definition color CCD camera HQ-1600 for the highest quality images

The high-definition color CCD camera HQ-1600 boasts a resolution of 1300/1500 TV lines. In combination with the Nikon HD Picture Adapter PA-160, the HQ-1600 can deliver image output on high-definition or multi-preset resolution TV monitors in real time. This is ideal for producing high-definition still images and building high-definition image database applications as well as other medical and industrial applications.


HQ-1600

Much higher image quality
Employing a 1-inch HD image pickup device, the HQ-1600 gives you high resolution images of 1300 TV lines (for HQ-1600S) and 1500 TV lines (for HQ-1600X). The RGB rotating disk system yields high-speed image capture as fast as one frame per 0.3 sec.

ENG mount or F mount model available
An ENG mount model for mounting on a microscope and an F mount model for shooting are available. A variety of Nikkor lenses can be mounted on the F mount model.

Supporting aspect ratio of 4 : 3
Depending on the TV monitor in use, aspect ratio of 16 : 9 or 4 : 3 (factory set) is available.

s high-speed image capture, paving the way the medical and industrial fields.

High-definition picture adapter PA-160 series

The PA-160 series is a system expandable picture adapter equipped with a video output (G/Y,B/Pb,R/Pr) terminal, RS-232C and SCSI interfaces*. The PA-160 series converts video signal from the HQ-130C/HQ-1600 into RGB composite signals, and delivers these signals to any high-definition TV monitor or monitors with preset resolutions, or other systems with RS-232C or SCSI interface. The video output (G/Y,B/Pb,R/Pr) terminal and the SCSI interface comply with the high-definition studio standard BTA S-001.

*Video output (G/Y,B/Pb,R/Pr) terminal and RS-232C interface are provided on all models as standard equipment. SCSI interface is on the PA-160D/EM/NR.

PA-160

Freeze function

Turning ON the freeze switch keeps the output image frozen on the monitor facilitating long-time image observation. Turning OFF the freeze switch delivers video signals to the monitor in real time.

Electronic pointer

A mouse-controlled electronic pointer is provided as standard equipment. You can choose your favorite shape and color of pointer. This is an effective presentation tool.

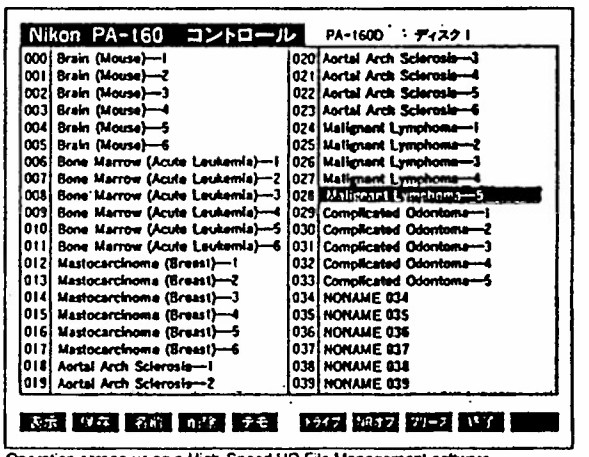
A variety of lineups to suit any application

The PA-160M (with 6 MB additional memory), featuring a video output (G/Y,B/Pb,R/Pr) terminal, is available in addition to the standard model PA-160. As for lineup models with a SCSI interface, the standard model PA-160D, the PA-160EM (with 6 MB additional memory), and the PA-160NR (with noise-reduction) are also available.

High-speed filing capability

Using NEC PC-98 series, EPSON PC-98 compatible computers as a controller, and a High-Speed HD File Management software, you can store (or retrieve) high-definition-based band images in approx. 2 sec. on (or from) a large capacity hard disk drive connected to the SCSI interface on the PA-160D/NR/EM. Displaying retrieved images on the high-definition TV monitors or monitors with multi-preset resolution is easy with a one-touch operation. With the automatic demonstration function, you can easily perform high-definition slide shows of the images stored in memory.

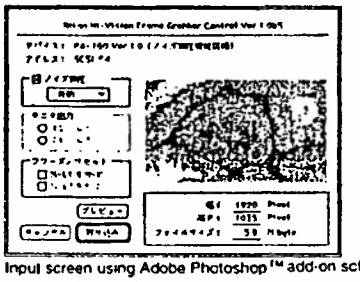
*500 MB hard disk drive has a storage capacity of approx. 80 images. A hard disk drive featuring high-speed access time is recommended.



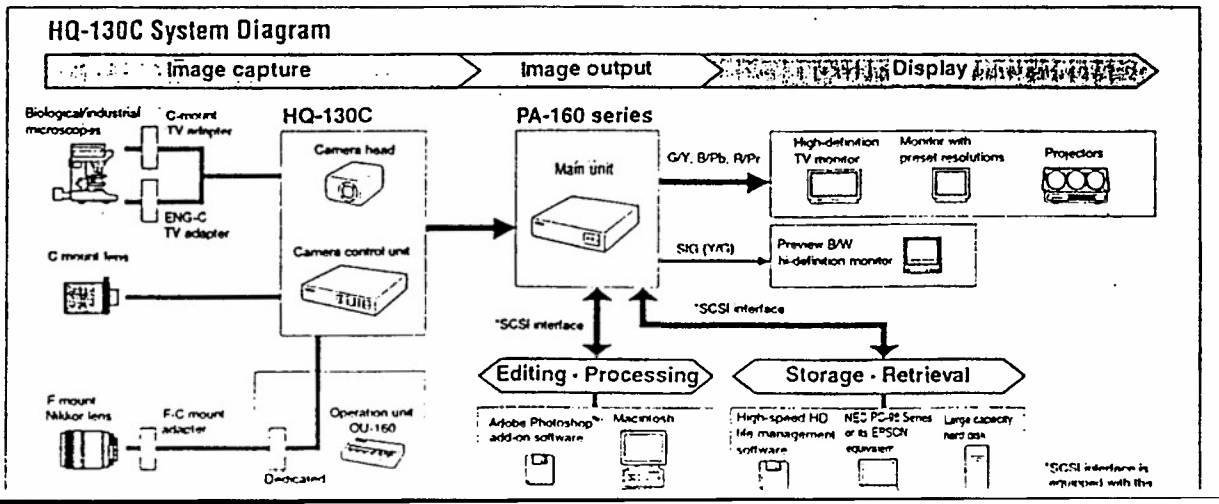
Operation screen using a High-Speed HD File Management software. Attached to the PA-160D/NR/EM

Image output to Apple Macintosh® computers

With Adobe Photoshop™ add-on software for the SCSI interface of the PA-160D/NR/EM, you can input digital image data with 1920 x 1035 or 1840 x 1035 pixel resolution to a Macintosh computer at high speed. Once the data is brought inside the computer, you can freely edit, modify or process the image, and output the image data to high-definition TV monitors or other monitors with preset resolutions.



Input screen using Adobe Photoshop™ add-on software.



Specifications HQ-130C

Image pick-up device	2/3" CCD (1,300,000 pixels)
Scanning system	1125 lines; 2:1 interlaced (conforms to BTA S-001)
Scanning frequency	Horizontal: 33.75kHz; Vertical 60.00Hz
Image capture speed	0.05 sec./frame (when detecting motion); 0.1 sec./frame (when not detecting)
Resolution	700 TV lines (using P-200 chart)
Lens mount	C mount
Aspect ratio	16 : 9
S/N ratio	50 dB or more
Sensitivity	2000 Lx/1/4 (3200°K), +6dB up 2000 Lx/1/5.6 (3200°K)
Sync signal	Int./ext. autoswitch (gen-lock circuit built-in)
White balance	Automatic (can be manually compensated)
Output signals	Video : 0.7 Vp-p/75Ω, RGB rotating disk (BNC) Sync : ±0.3 V/75Ω, 3-value SYNC (BNC) Color-code : TTL level (D-sub 9P)
Camera cable	Standard: 5m (optional: 2m/10m)
Power source/ consumption	AC 100V/0.45A
Weight	Camera head: 500g Camera control unit: approx. 5kg

PA-160 Series

		PA-160	PA-160M	PA-160D	PA-160EM	PA-160NR
Memory (max.)		6 MB (1 frame)	12 MB (2 frames)	6 MB (1 frame)	12 MB (2 frames)	6 MB (1 frame)
Output signal	Standard	BTA (conforms to S-001)				
	Video signal	G/Y; B/Pb; R/Pr (selectable by switch)				
		Y/G 0.7 Vp-p/75Ω positive, SYNC is fixed by Y/G signal-added; 0.3V/75Ω negative				
	Sync signal	SYNC ±0.3 V/75Ω 3-value (BNC) HD 1.8 Vp-p/75Ω negative (BNC) VD 1.8 Vp-p/75Ω negative (BNC)				
	SCSI interface			Conforms to SCSI-II (50-pin half-pitch connector×2) Term-power ON/OFF		
	Digital conversion system (sampling frequency)			74.25 MHz (BTA 1920 × 1035 pixels) 71.28 MHz (SQUARE 1840 × 1035 pixels)		
Noise reduction						Available (ON/OFF)
Power source		AC 100V ±10% 50/60Hz				
Power consumption		1.2A	1.5A	1.5A	1.6A	1.6A
Weight		8.7kg	9.2kg	9.2kg	9.5kg	9.7kg

High-Speed HD File Management Software

System required	Computer	NEC PC-98 series/EPSON PC-286/386/486 series
	Operating environment	MS-DOS 3.3 or later; 640 kB RAM or more; RS-232C interface
	Hard disk	Fast SCSI; 500 MB or more; transfer rate: 10 MB/sec or more
	Cable	RS-232C cable (reversed) SCSI cable (high-impedance) Connector: 50-pin half-pitch for PA-160 Appropriate type for hard disk SCSI terminator
Main functions	Input	• Function keys • Mouse-driven image file selection • Image freeze ON/OFF
	Edit	• Image file naming • Image file sorting • Hard disk selection
	Image output	• Next image selection using programmed mouse button • Random image selection using cursor • Auto-demo (time: 2 to 999 sec.)

Adobe Photoshop™ Add-On Software

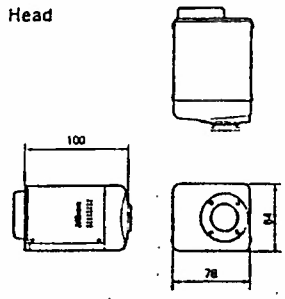
Computer		Macintosh with 68020 CPU or higher
System required		System 7/Kanji-Talk 7 or later; 8 MB RAM or more; 100 MB hard disk (more recommended); 24-bit video card; full-color monitor; Adobe Photoshop™ 2.0J or later
Main functions	Input	• Freeze/Preview/Cropping • Noise reduction ON/OFF *1 • Noise reduction mode selection *1
	Output	• G/Y; B/Pb; R/Pr (selectable by switch) • 2-image selection *2

*1: PA-160NR only
*2: PA-160EM only

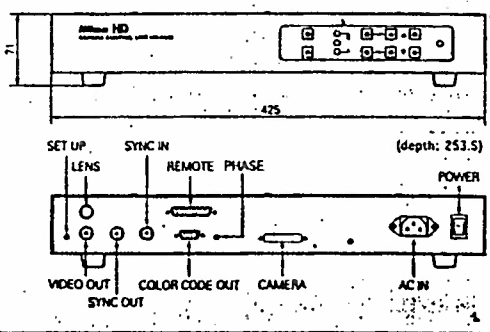
NIKON CORPORATION
Planning Section, Electronic Imaging Division
4-25, Nishi-Ohi 1-chome, Shinagawa-ku, Tokyo 140, Japan
Tel : +81-3-3773-8105 Telex : 22601 (NIKON J)
Telefax : +81-3-3773-8117

■Dimensions (unit: mm) A73

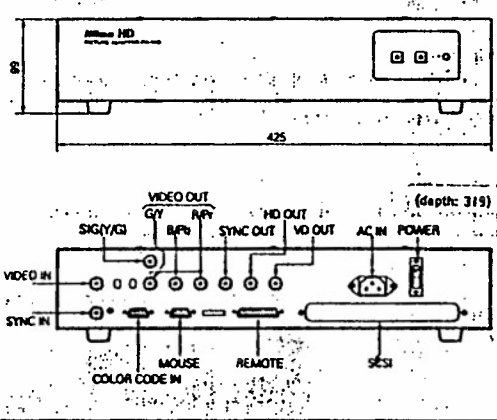
HQ-130C Camera Head



HQ-130C Camera Control Unit



PA-160 Series (unit: mm)



■System Configuration

HQ-130C	Camera head; camera control unit; camera cable set
PA-160/M	Main unit; video cable set
PA-1600/NR/EM	Main unit; video cable set; High-Speed HD File Management Software

Nikon Inc
1300 Walt Whitman
Melville NY
11747

Nikon A952 Project
1-4-25, Nishi-Ohi, Shinagawa, Tokyo, 228 JAPAN
Phone: 3-3773-8125, Fax: 3-3773-8118

Date: Dec. 12, 1995
To: Dr. Brian Athie, Univ. Michigan
From: Atushi Kayukawa、Nikon
CC: Mr. Lee Shuett
RE: Nikon's visit
Fax # : 313/763-1166
# of Pages including the cover : 9

Dear Dr. Athie:

This is to follow up Mr. Shuett's phone call on the possible collaboration between U. Michigan and Nikon to develop a telepathology system.

As he mentioned in his telephone conversation, Nikon's high quality image network system for telemedicine and medical teleconference has been accepted favorably in Japan. And now we are seeking an opportunity to expand our business abroad and to collaborate with leading research institutes such as U. Michigan. We like to come to your office and have a discussion on the following topics.

Proposed agenda of the meeting

1) The use of Nikon's network system at the National Cancer Center
A video summary of a recent medical conference.
2) Introduction of the Nikon's telepatology system
The key ingredient of our system is the use of high resolution imaging devices. Those include 1.3 M pixel CCD movie and still cameras which are manufactured by Nikon, and 2000x1000 display of other parties.
3) Discussion on the collaboration.

I'd like visit you some time in the second half of January. Let me know your availability of that month.

With this message, I am sending two papers which describes a part of Nikon's National Cancer Center project. Excuse me for some hand writting on them.

Best regards,

Atushi Kayukawa

16. Experience in Telecytodiagnosis

Kimie Yamagishi[1], Takeo Matsumoto[2], Yukako Yagi[3], Tetsuro Kodama[2] and Yukio Shimosato[4]

ABSTRACT

This report dealt with accuracy of cytodiagnosis made from celluler images on the video monitor of 60 cytological specimens.
We used both high definition television (HDTV) still image with 1125 scan lines and the National Television Committee (NTSC) still image with 525 scan lines. Times required for diagnosis on an image transmitted through INS 64 (the integrated services digital network 64 Kb/s) were three to seven minutes by observing HDTV still image and one minute by the NTSC still image. Diagnostic accuracies were 97.4% with the use of HDTV, and 90.9% with NTSC.
These telecytopathology system were found to be very effective in correct interpretation of cytological findings and useful for both clinical cytology practice and consultation of difficult cases.

Telecytopathology is a new arm, with which cytopathologists can provide services within and between medical facilities. Telecytopathology is a branch of telemedicine, which is defined as use of the tele-network to transmit medical information. With this system using an integrated services digital network system, high-resolution video cameras atteched to a remotely controllable microscope and monitors, it is now possible to communicate through the video-image with a cytopathologist or cytologist remote from the station.
This paper dealt with the result of our experimental trial of telecytodiagnosis.

MATERIALS AND METHODS

In order to evaluate the diagnostic accuracy, usefulness and disadvantages of the telecytopathology system, we used two kinds of video images, which were the high

1. Pathology Division, National Cancer Center Research Institute, Tokyo
2. Clinical Laboratory Division, National Cancer Center East Hospital, Chiba,
3. Instruments Division, Nikon Co., Tokyo,
4. Clinical Laboratory Division, National Cancer Center Hospital, Tokyo, Japan

definition television (HDTV) still images on a monitor with 1125 scan lines and images of the National Television Committee (NTSC) system on a conventional monitor with 525 scan lines. The video images were transmitted through an integrated services digital network system {ISDN, INS 64 (64Kb/s)} from the National Cancer Center East Hospital to the National Cancer Center Hospital (Fig. 1), the distance between these two hospitals being about 30 kilometers. Using the HDTV still images transmitted through ISDN, INS 64, 38 cytological specimens were examined including 11 from benign lesions and 27 from malignant lesions. For the NTSC still images 22 cases were examined including three benign and 19 malignant lesions.

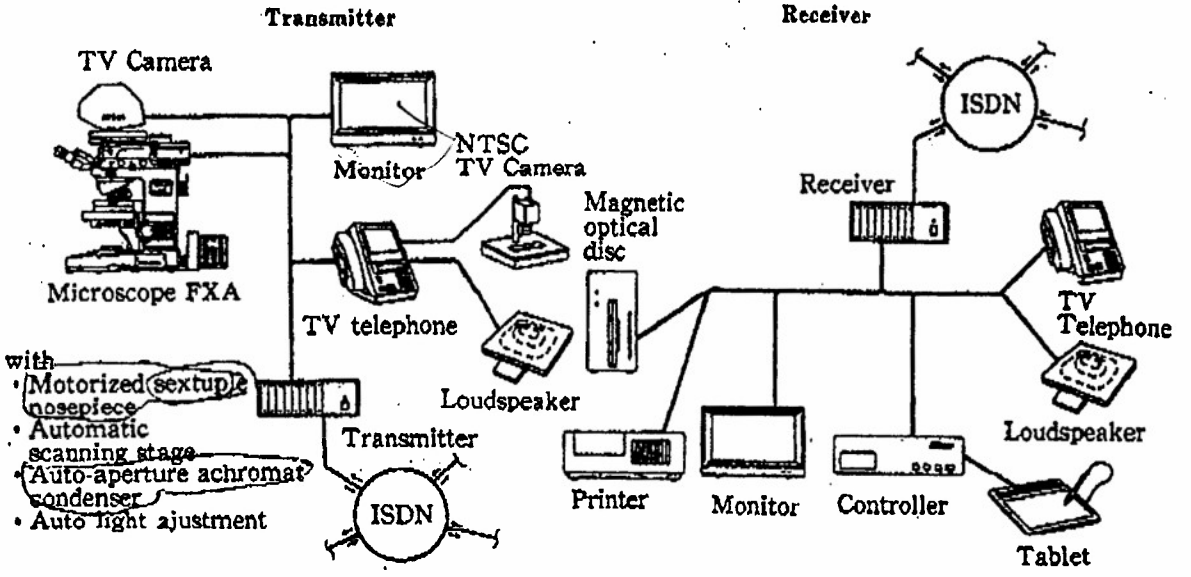


Fig. 1 Telecytology system using ISDN

In these experiments, information on the specimen was limited to ID number, sex, age, method of sampling and clinical diagnosis.

We used video telephone with a loud-speaker to communicate between the trasmitter and receiver.

RESULTS

1. Time for video image transmission

With the use of ISDN, INS 64 system, it took 100 seconds to transmit a single HDTV still image and 20 seconds per one NTSC still image, respectively (Table 1).

2. Time for diagnosis

Using the HDTV still image, it took three to seven minutes to make diagnosis on two to four video-images from a single case. With the NTSC still image, it took one

minute to establish diagnosis on two to four video images from a single case. Because of the time-consuming procedure, the average number of video images were limited to three per case (Table 1).

3. Cytological diagnosis of malignancy on a video monitor compared with conventional microscopic diagnosis

Using the HDTV image, cytological diagnostic concurrence ratio as compared with a conventional microscopic diagnosis was 94.8%, which increased to 97.4% when diganoses within a permissible range were included. Diagnoses within a permissible range meant those not affecting choice of therapy. Using the NTSC image, diagnostic concurrence ratio as compared with microscopic diagnosis was 90.9% (Table 2).

Table 1 Telecytology system

Media	Video image	Scan lines	Time for trasmission second /still image	Time for diagnosis minute /case	No. of cases examined	Diagnostic accuracy %
ISDN INS 64 (64kb/s)	HDTV still image	1125	100	3-7	38	97.4
	NTSC still image	525	20	1	22	90.0

Table 2 Telecytology diagnosis with regard to malignancy of lesions

Video image	Materials	No. of cases	No. of correct diagnosis	No. of permissible diagnosis	No. of incorrect diagnosis
HDTV	Benign lesions	11	9	1	1
	Malignant lesions	27	27	0	0
	Total	38	36(94.8%)	1(2.6%)	1(2.6%)
NTSC	Benign lesions	3	3	0	0
	Malignant lesions	19	17	0	2
	Total	22	20(90.9%)	0(0%)	2(9.1%)

4. Interpretation of nature of lesions

Using the HDTV image, percentage of concurrence compared with conventional microscopic cytodiagnosis was 97.4%, including correct diagnosis and that diagnosis within permissible range. One case with misinterpretation on the HDTV image was uterine cervical dysplasia, in which cytological atypia was considered due to Herpes simplex infection. Lesions evaluated correctly or permissiblly by the HDTV were as follows; eight adenocarcinomas, seven transitional cell carcinomas, six cervical dysplasias, four squamous cell carcinomas, two malignant lymphomas and cervical carcinoma in-situ, one malignant mesothelioma, carcinoid tumor, large cell carcinoma, small cell carcinoma, ependymoma, mammary intraductal papilloma, endometrial cells, and candida.

Using the NTSC image, concurrence ratio was 72.7%, including correct diagnosis and that within permissible range. Six cases misinterpreted on the NTSC images were as follows; malignant mesothelioma in pleural effusion was incorrectly diagnosed as reactive mesothelial cells; adenocarcinoma of the breast in needle aspiration was considered fibroadenoma; adenocarcinoma in duodenal dranage was cytologically considered squamous cell carcinoma; metastatic adenocarcinoma from colon cancer obtained by bronchial brushing was considered as squamous cell carcinoma; squamous cell carcinoma in bronchial brushing was cytologically diagnosed large cell carcinoma; and small cell carcinoma of the lung in needle aspiration smear was cytologically diagnosed as squamous cell carcinoma non-keratinizing type. Discrepancy between interpretation on the video monitor and the conventional microscopic interpretation were frequent on the NTSC images (Table 3).

Table 3 Cytological interpretation on video image

Video image	Materials	No. of lesions	No. of correct diagnosis	No. of permissible diagnosis	No. of incorrect diagnosis
HDTV	Benign lesions	11	10	0	1
	Malignant lesions	27	24	3	0
	Total	38	34(89.5%)	3(7.9%)	1(2.6%)
NTSC	Benign lesions	3	3	0	0
	Malignant lesions	19	11	2	6
	Total	22	14(63.6%)	2(9.1%)	6(27.3%)

5. Quality of image on video monitor

The quality of the HDTV still image was far superior to the image of NTSC, although resolution was not enough to observe cellular detail when compared with the image under the microscope. For examination of cells, a 20X, 40X and 60X objective lens were efficient. A 10X objective lens was not high enough to observe cellular morphology.

6. Cost of image transmission

Through ISDN, INS 64, the transmission fee was 950 yen per one hour, and the contract cost was 5400 yen per one month.

DISCUSSION

This telecytopathology system was found to be very effective in correct interpretation of cytological findings and in making diagnosis, since only cells of special interest were transmitted for evaluation by a consultant. In Mayo Clinic, the dynamic telepathology system was designed for frozen and permanent sections of pathological specimens and for cytology specimens. According to them, video image quality of permanent sections was in general not the limiting factor in establishing a correct diagnosis. Cytologic preparations were likewise generally easily interpreted. Frozen sections, however, were more difficult to interpret. Therefore this system is not suitable at present for intraoperative frozen section diganosis and for cases in which it requires few minutes or more for microscopic observation to reach a diagnosis.

The current major utility of telepathology is the diagnostic support to a site remote from the principal station, which is followed by continuing education. However, telecommunication should be done for consultation purpose between pathologists, transmission from a hospital without pathologists should be avoided.

The legal problem may arise from misdiagnosis made on video images. Since the quality of the video image is far inferior to that of microscopic images, a slight increase in the rate of misdiagnosis made on video image is expected. Misinterpretation of the tumor type on the monitor is due largely to the quality of the image, experience with video image interpretation, and the ablity of the observer.

In the near furture, when INS 1500 (1.5Mb/s), which requires only several seconds for transmission of a single HDTV image, becomes available, it will be used even for intraoperative frozen section diagnosis.

In conclusion, the telecytopathology was found to be very effective in cytological diagnosis and consultation of difficult cases.

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Cytological diagnosis through video image; an attempt of quality assurance program

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Summary

An interobserver variability of a cellular evaluation through video images was described. Eleven cytotechnologists examined the video display images of eleven cases of intraoperative lavage cytology smears which were stained by PAPANICOLAOU method, independently. In most cases, the eleven cytotechnologists differed somewhat in suggestive diagnoses. Between observer variability was not correlated with the year of experience in cytotechnology. Undercalled diagnosis and undetermined diagnosis were made by not only junior cytotechnologists but also senior cytotechnologists.

Introduction

The use of cytology in pathologic diagnosis has increased the last two decades. Computerization of record keeping and reporting systems in medical institutions is unavoidable. Computerized quality assurance mechanis are desirable. Quantitative and analytical cytology are preferable and should provide success in objectifying our cellular evaluations. A subjectivity of the cytologic diagnosis causes a significant variation between observers and within an observer. The observers are influenced by internal and external factors. A fully automated diagnostic cytology system is not and will not become a useful routine system in the near future. On the other hand, an interactive cytology automation will become such an instrument. Thus uniformity in our cellular identification is the most important thing.

By using a high resolution video image, we attemped to reduce the interobserver variability.

Telemedicine is no longer a futuristic means but provides service for us in these days. Telepathology is currently being employed on a daily basis between the National Cancer Center Central Hospital and the National Cancer Center East Hospital, the distance between these two hospitals being about thirty kilometers.

This service is now possible due to high resolution video cameras and monitors, high definition television with 1125 scan lines (HDTV), telecommunication technique of video images, video conference system, microscope with motorized X, Y and Z stage movements, magnification and illumination and telenetwork with a six mega-bit per second capacity. The system in the Central Hospital allows

Suggested Video Image Diagnosis and Histological Diagnosis

Case no.	Cytotechnologists and Year of experience CT13	CT2	CT13	CT25	CT3	CT13	CT2	CT4	CT2	C16	CT25	Histological Diagnosis
1	A	A	A	AT	A	A	A	A	A	A	A	Papillary adenocarcinoma
2	A	A	B	A	A	A	A	A	A	A	A	Signet ring cell carcinoma
3	B	A	A	AT	A	A	A	A	A	A	A	Poorly differentiated adenocarcinoma
4	B	A	A	A	A	B	A	A	A	A	A	Signet ring cell carcinoma
5	A	U	A	A	AT	A	AT	A	A	A	A	Poorly differentiated adenocarcinoma
6	A	B	B	A	B	A	A	B	A	A	A	Mucinous adenocarcinoma
7	B	B	A	B	A	B	A	A	A	A	A	Tubular adenocarcinoma
8	A	B	A	B	AT	A	B	A	A	B	A	Tubular adenocarcinoma
9	B	B	B	U	A	A	A	A	A	AT	A	Poorly differentiated adenocarcinoma
10	B	AT	A	AT	B	U	A	A	B	A	A	Mucinous adenocarcinoma
11	B	B	B	B	B	A	B	B	B	A	A	Tubular adenocarcinoma
A	5	4	7	3	7	7	8	9	9	9	11	
AT		1		4	1	1	1			1		
U		1		1		1						
B	6	5	4	3	3	2	2	2	2	1		

A: Adenocarcinoma AT: Atypical cells B: Benign cells U: Undetermined

Papanicolaou stained video image from the case 11 and its anti-CEA reaction (above). Anti-BerEP4 positive cell group in the case 11 cytology smear and tubular adenocarcinoma with invasion of the serosa in the case 11 histological section (below).

Materials and methods

The eleven smears were used from the files of the National Cancer Center Central Hospital. cancer and stained by PAPANICOLAOU method. These stomach cancers penetrated

carcinoma cells. These cells were confirmed in all cases by morphological findings, immunocytostaining (anti-CEA, anti-BerEP4) reaction, alcian blue staining reaction. Giemsa staining and histological features.
One microscopial area on each smear was selected for the video image and taken three sets of views, low-powered (20x), medium-powered (40x), high-powered (60x).
The eleven cytotechnologists examined the video display images of the eleven smears independently. Years period as cytotechnologists were one for one year, three for two years, one for four years, one for six years, three for 13 years and two for 25 years.

Results

In all cases, the observers suggestive diagnoses differed and interobserver variability was not correlated with the year of experience in cytotechnology (Table).
Undercalled diagnoses and undetermined diagnoses were made by not only junior cytotechnologists but also senior cytotechnologists.
The quality of the video images of the high definition television was far superior to the images of the National Television System Committee (NTSC) on a conventional monitor with 525 scan lines. For examination of cells, the 40x and the 60x objective lens were efficient, the 20x objective lens was not high enough to observe cellular morphology. Time for the video image transmission was from three to five seconds per one image.

Discussion

In all cases except case 11, the smears contained cells that can be recognized as adenocarcinoma. In case 11, the smear contained cells in group which were anti-CEA and anti-Berep4 positive in immunocytostaining and resembled cytomorphology in appearance in histology preparations (Fig.).
At conventional screening, immunocytostaining (anti-CEA or anti-BerEP4), or alcian blue staining were useful to the interpretation of cells for the cytotechnologists. For all observers, it proved to be very important that the abnormal findings associated with the conventional smear of adenocarcinoma was not available on one image of microscopical area.
Using conventional microscope, percent concordant diagnoses between cytotechnologists was about 57 percent by Papanicolaou stained smears. Although, through the video image, percent agreement between cytotechnologists smears, more than 85 percent using immunocytostained smears. Quality assurance and education through the video image are best accomplished via less expensive means. In addition to telepathology, the video image used for conference within and between medical centers and for filling of images.

ICAM-1 and Integrin Expression on Isolated Human Alveolar Type II Pneumocytes

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Adhesion molecules are involved in the recruitment of leucocytes to sites of inflammation. In this study, we determined the expression of several adhesion molecules on isolated human alveolar type II pneumocytes.
Type II pneumocytes were isolated from 10 normal lung specimens, by enzymatic digestion with dispase, followed by metrizamide gradient centrifugation and planning on immunoglobulin G (IgG)-coated plastic dishes. With the freshly isolated type II cells, immunostatining was performed using a sensitive immunoperoxidase slide technique.
In all cases, 60-90% of type II cells were positive for intercellular adhesion molecule-1 (ICAM-1) (CD54). A minor portion of type II cells expressed the alpha 4 (CD49d) subunit of the β1-integrins, and the alpha-v (CD51) subunit of the vitroectin receptor. CD11a, CD11b, CD11c, CD18, CD49b, CD49e and CD49f failed to demonstrate any immunostaining with type II cells.
In conclusion, the observation of the expression of ICAM-1 and, to a lesser degree, of some integrin subunits, may indicate that alveolar type II cells participate in local immune and inflammatory responses.

This paper has been published in European Respiratory Journal:
Eur Respir J 1994, 7, 736-739

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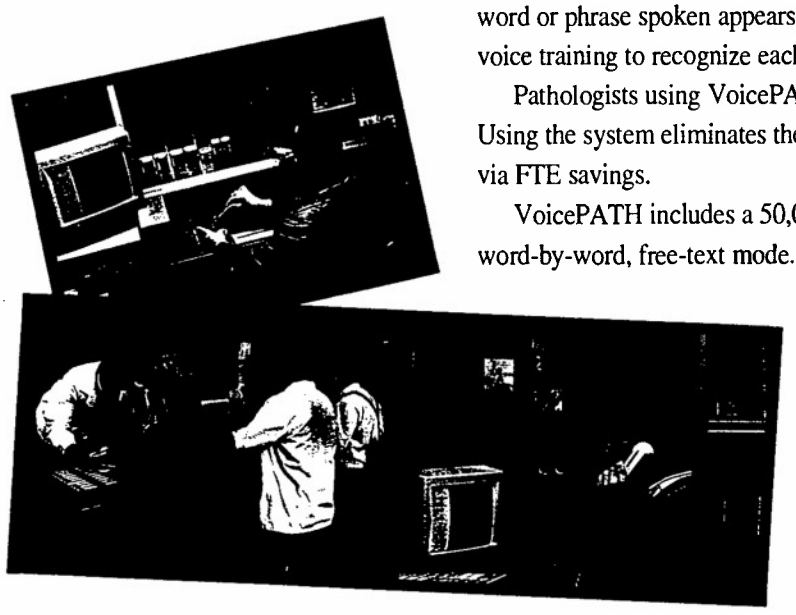

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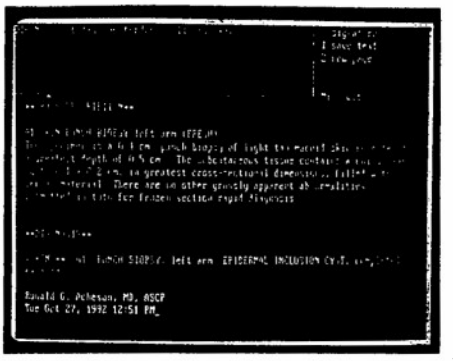
VoicePATH can be integrated with a laboratory or hospital information system to deliver reports to clinicians and all hospital departments, including billing and reimbursement departments, which can enhance cash flow.

[1] *Kempson et al, Am J Surg Path. Vol. 16, No.1, page 84 (1992)*

VoicePATH® Reports

Surgical pathology reports can be generated, by incorporating word-by-word dictation, trigger phrases and the underlying report framework to generate gross descriptions for surgical pathology reports in the following categories:



- *Bones and Joints*
- *Breast*
- *Cardiovascular*
- *Endocrine Organs*
- *ENT Region*
- *Female Reproductive/GYN*
- *Gastrointestinal*
- *Lympho Hematopoietic System*
- *Male Reproductive*
- *Mediastinum*
- *Nervous System*
- *Oral*
- *Respiratory*
- *Skin and Subcutaneous Tissues*
- *Soft tissue*
- *Urinary*

Microscopic diagnoses and comments can be dictated either by using the 50,000 word free-text capability, or by using the built-in trigger phrases which are useful for prompting physicians for quality assurance content.

Barrington General Hospital
Department of Pathology

S92-162334 Medical Record Num: 12369
Smith, Mary K. DOB: 05/04/54

GROSS DESCRIPTION

A. SKIN PUNCH BIOPSY left side of nose (FORMALIN): The specimen is a 0.8 cm. punch biopsy of red-tan hairless skin resected to a greatest depth of 0.2 cm. The peripheral margins are inked in black. Submitted in toto for frozen section rapid diagnosis.

FROZEN SECTION DIAGNOSIS: FIBROSIS.

DIAGNOSIS
SKIN ** A: PUNCH BIOPSY: left side of nose:
FIBROUS PAPULE OF THE NOSE Completely excised.

Andrew Marshall, M.D.,
Thu Oct 22, 1992 10:09 AM

BENEFITS

- **Immediate Reports** - no waiting for transcription, 24 hours per day, 7 days per week
- **Productivity** - improves throughput by bypassing clerical bottlenecks and staff shortages
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FEATURES

- **No Voice Training Required** - the system automatically recognizes accents and speech patterns
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- **200,000 Word On-Line Intelligent Search Dictionary** - The American Heritage Dictionary
- **Pre-defined Knowledge Base** - designed by practicing pathologists to include words, phrases and terms used in today's anatomic and surgical pathology reports
- **Instant Response** - each word or phrase is instantly displayed on the monitor as it is spoken
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- **Intelligent Trigger Phrases** - a single spoken word or phrase can trigger an entire pre-defined report segment, with "fill-in-the-blank" capability for individualization
- **Flexibility** - reports can include word-by-word dictation and the vocabulary can be customized to meet individual reporting requirements
- **Spoken Commands** - reports can be edited by voice and printed by saying "print report," or sent to the laboratory information system
- **Multiple Users** - a system can be shared by several physicians, each with his or her own customized vocabulary (the system is active for one user at a time)
- **Edit/Cut and Paste** - easily edit any report while you are dictating
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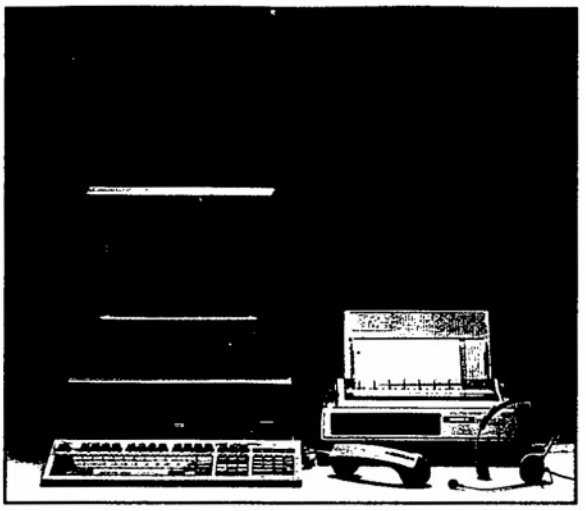
HL-7 Interconnect Capability

- **VoiceFAX™ Option** - fax reports directly to clinicians



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